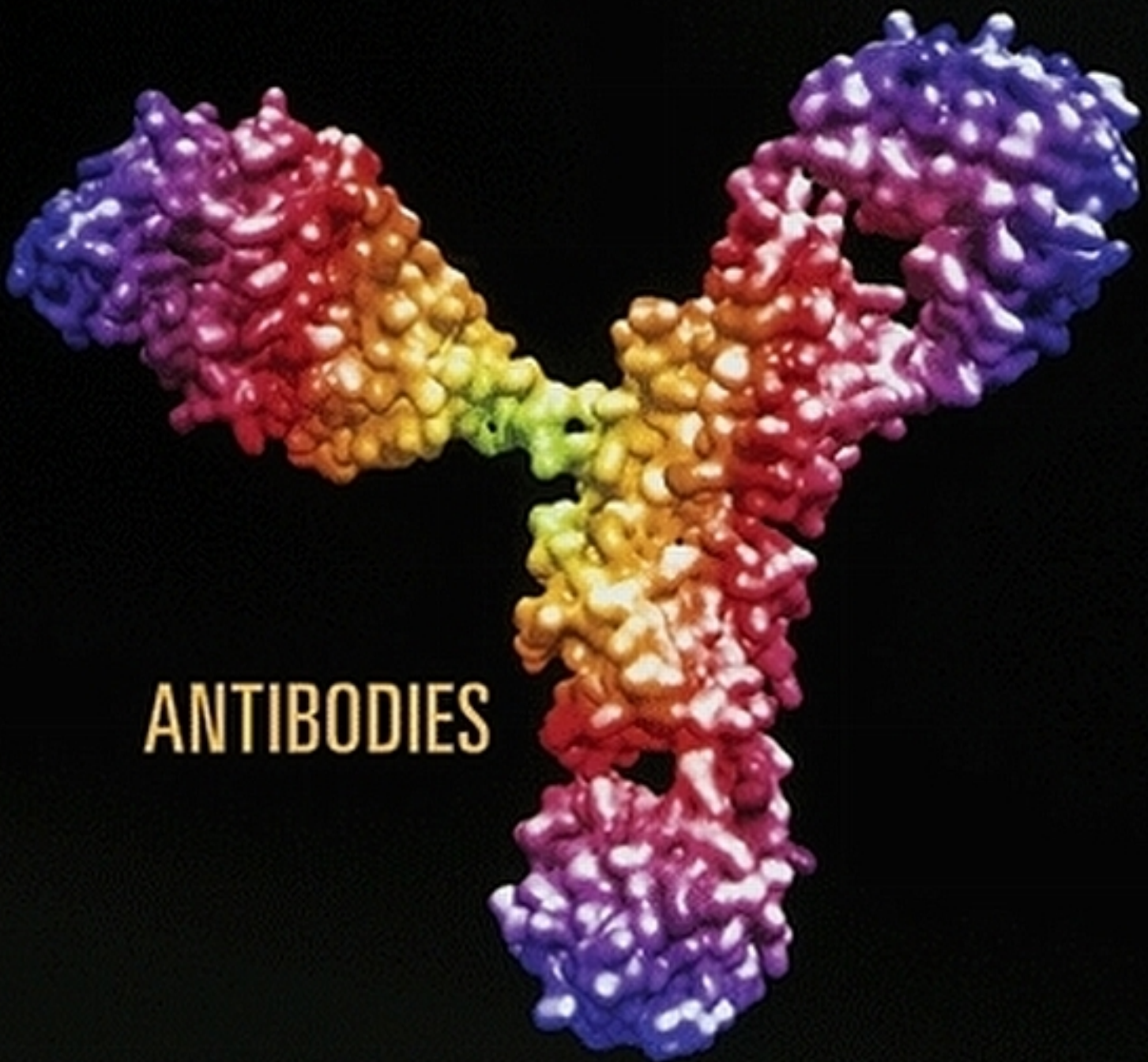
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Science



ANTIBODIES

AAAS

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Antibodies

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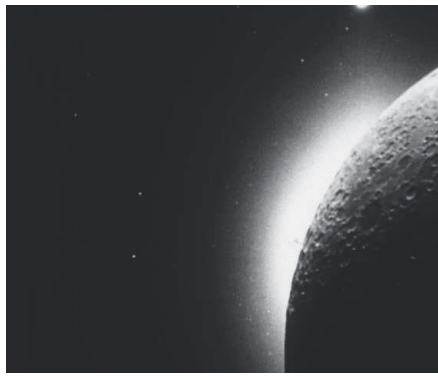
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COVER

Structural model showing the electron density surface of immunoglobulin G, a major antibody subtype. The human immune system generates a diversity of these Y-shaped antibodies that recognize foreign molecules and directly neutralize the targeted invaders or tag them for destruction. Antibodies that bind one or more specific targets are being harnessed in the treatment of disease and are informing vaccine design. See page 1191.

Image: Alfred Pasieka/Science Source

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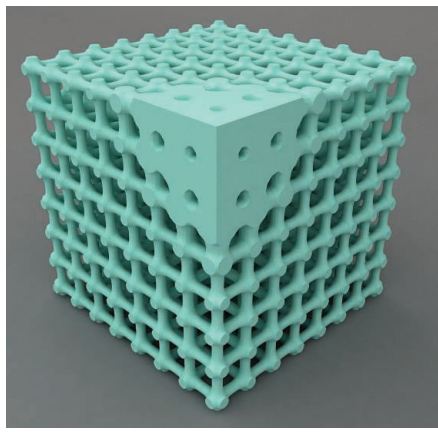
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EDITED BY CAROLINE ASH

Climate and Conflict

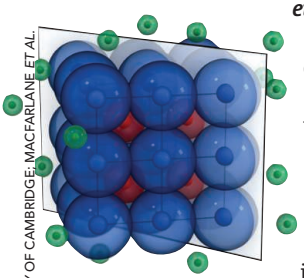
Knowledge silos can hinder attempts to explore questions of interest across many disciplines. **Hsiang *et al.*** (p. 1212, published online 1 August) provide a meta-analysis of data from disciplines as disparate as archaeology and psychology to examine the relation between climate and conflict. Overall, warmer temperatures or extremes of rainfall can be causally associated with changes in interpersonal violence and in civil war.

Tick, Tick, Tick…

Many aspects of everyday life from communication to navigation rely on the precise ticking of the microwave transitions of the atoms in atomic clocks. Optical transitions occur at much higher frequency and so offer the opportunity to reduce the scale of the ticks even more. **Hinkley *et al.*** (p. 1215, published online 22 August; see the Perspective by **Margolis**) compare the ticking of two optical clocks and report an instability near the 10^{-18} level. Such performance will improve tests of general relativity and pave the way for a redefinition of the second.

Sticking with DNA

One strategy for creating superlattices from nanoparticles is to coat the particles with DNA strands that have sticky ends that can be exploited to control the assembly of the lattice. This method can create binary lattices, but now **Macfarlane *et al.*** (p. 1222, published online 22 August) have succeeded in inserting a third type of nanoparticle into a predetermined site by tuning the strength of the relative DNA binding interactions.



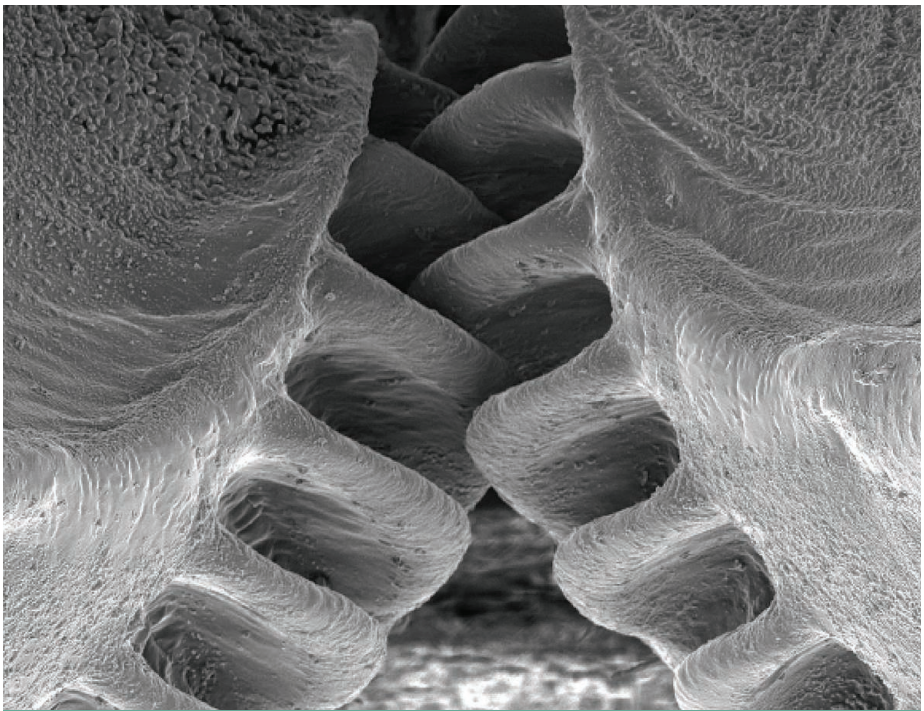
CREDITS (TOP TO BOTTOM): M. BURROWS/DEPARTMENT OF ZOOLOGY, UNIVERSITY OF CAMBRIDGE; MACFARLANE *ET AL.*

Catalytic Parachute

Small organic molecules have emerged as catalysts as versatile as transition metal complexes. However, industrial application of such organocatalysts has been hampered by technical challenges. Now **Lee *et al.*** (p. 1225) have succeeded in tethering a diverse set of high-performance organocatalysts to nylon fabric through ultraviolet photochemistry, making them easy to isolate and reuse.

Slow Stick-Slip

While the character of slow earthquakes has been approximated for some time, precise slip histories and the underlying mechanisms have remained elusive. **Kaproth and Marone** (p. 1229; published online 15 August) have made laboratory observations of repetitive, slow stick-slip in fault-zone materials and developed a mechanical explanation for how earthquake-like dynamic slip nucleation could start and then arrest so as to produce slow slip. As preseismic slip is a precursor to rupture, temporal variations in elastic wave speeds should be monitored in regions of high seismic hazard.



Joint Action

Many small insects are impressive jumpers, but large leaps and small bodies pose biomechanical challenges. **Burrows and Sutton** (p. 1254) show that the nymphal planthopper *Issus* has interlocking gears on their hindleg trochanters that act together to cock the legs synchronously before triggering forward jumps. At the final molt, the gears are swapped for a high-performance friction-based mechanism because the risk of breaking a gear is high, the options for repair during molting are gone, and, moreover, the animal is bigger and stronger.

Local Speeding

Early responses of species to climate change seemed to predict a general poleward response (or upward in mountains and downward in the ocean). **Pinsky *et al.*** (p. 1239) test an alternative hypothesis that relates more to the nature of climate change than to changes in temperature. Using nearly 50 years of coastal survey data on >350 marine taxa, they found that climate velocity was a much better predictor of patterns of change than individual species' characteristics or life histories. The findings suggest that responses to climate change largely track changes in local conditions.

Move Over, TLR4

The innate immune system senses bacterial lipopolysaccharide (LPS) through Toll-like receptor 4 (TLR4) (see the Perspective by **Kagan**). However, **Kayagaki *et al.*** (p 1246, published online 25 July) and **Hagar *et al.*** (p. 1250) report that the hexa-acyl lipid A component of LPS from Gram-negative bacteria is able to access the cytoplasm and activate caspase-11 to signal immune responses independently of TLR4. Mice that lack caspase-11 are resistant to LPS-induced lethality, even in the presence of TLR4.

From Soil to Sky

Trace gases emitted either through the activity of microbial communities or from abiotic reactions in the soil influence atmospheric chemistry. In laboratory column experiments using several soil types, **Oswald *et al.*** (p. 1223) showed that soils from arid regions and farmlands can produce substantial quantities of nitric oxide (NO) and nitrous acid (HONO). Ammonia-oxidizing bacteria are the primary source of HONO at comparable levels to NO, thus serving as an important source of reactive nitrogen to the atmosphere.

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Additional summaries

Quality Ultralight

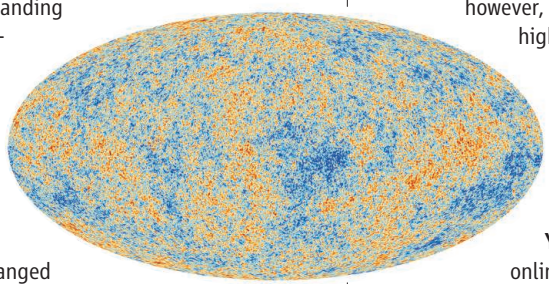
Ensuring the light-weight and high-strength properties of carbon-fiber composite materials is costly. **Cheung and Gershenfeld** (p. 1219, published online 15 August; see the Perspective by **Schaedler *et al.***) have mass-produced cross-sectional parts that can be assembled into strong, ultralight lattices. Carbon-fiber composites are sliced into cross-shaped pieces that can be independently tested and reliably assembled into rigid and reversible cuboctahedral lattices.

Active Ice

How, exactly, does warm ocean water erode an ice shelf? In a field study of an ice shelf at Pine Island, Antarctica, **Stanton *et al.*** (p. 1236) collected data from radar, seismic surveys, and oceanographic sensors inserted in holes bored through the ice shelf. The results show that localized, intensive melting occurs in a complex network of discreet channels that are formed on the underside of the shelf. This pattern of melting may limit the absolute rate of ice-shelf mass loss.

Tinyverse

Quantum many-systems, such superfluids, are difficult to study in equilibrium, and thus understanding their dynamics poses a particular challenge. When the strength of interactions was suddenly changed in a two-dimensional gas of cesium atoms, **Hung *et al.*** (p. 1213, published online 1 August; see the Perspective by **Schmiedmayer and Berges**) observed oscillations in the time and space domains analogous to the peaks in the spectrum of the cosmic microwave background.



CREDIT: EUROPEAN SPACE AGENCY/PLANCK

At a Stretch

Insect flight muscles are operationally similar to vertebrate skeletal muscles in many ways; however, they are specialized for high-speed, small amplitude oscillations and are activated not by the release and re-uptake of calcium, but rather through stretch-activation. **Iwamoto and Yagi** (p. 1243, published online 22 August) use a pair of ultrafast cameras to record diffraction patterns and wing beats in the flight muscles of bumblebees and find that stretch activation is a result of myosin and actin dynamics.

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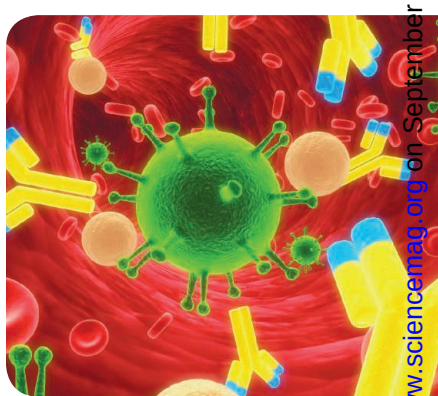


Translating Antibody Insights

Julie Louise Gerberding is president of Merck Vaccines at Merck & Co. (which develops drugs and vaccines for the treatment and prevention of infectious diseases; J.L.G. owns stock in the company); an associate adjunct professor of Medicine (Infectious Diseases) at the University of California, San Francisco; and a former director of the U.S. Centers for Disease Control and Prevention. E-mail: Julie.Gerberding@merck.com.

VIRUSES THAT DEFY HOST IMMUNE RESPONSES AND PERSIST OR RECUR TAKE A HUGE TOLL ON GLOBAL human health. Many of these, including HIV-1, influenza viruses, and several flaviviruses (such as dengue, hepatitis C, and West Nile virus) rapidly proliferate, frequently mutate, and evolve highly variable surface structures. The effectiveness of such immune escape mechanisms has thwarted multiple attempts to create long-lasting and broadly protective vaccines.

Nevertheless, these pathogens are not invulnerable. Key surface regions of the virus are constrained by requirements for precise interactions with the host cell that allow viral entry. These domains can contain antigenic determinants (epitopes) that elicit broadly neutralizing antibodies (bNAbs) from immune cells (B cells) in the infected host, even to highly variable viruses. Characterization of these bNAbs is accelerating because of improved approximations of the three-dimensional structure of antibody-binding sites on the virus surface, new tools for efficient detection of specific bNAbs from immune cells, and longitudinal studies of the evolution of antibody production by B cells during the immune response (B cell affinity maturation).



The ultimate goal is to identify antigens for "universal" vaccines that provoke long-lasting memory B cells that neutralize all relevant virus variants and provide protection from infection. Unfortunately, this is easier said than done. A major challenge is delineating the nature of the epitopes of interest. The important viral epitopes recognized by bNAbs to HIV-1 and influenza tend to be nonlinear, sequestered from the reach of most antibodies, a minor component of the total antibody response, and represent only a small portion of the conserved virus structures. Thus, it has been difficult to convert these epitopes into stable vaccine antigens that elicit the intended protective antibodies. In addition, mutations in these epitopes that escape recognition by bNAbs may eventually appear. Furthermore, bNAbs usually develop later in chronic infections and often have complex atypical configurations in their variable regions. Strategies to induce and shape the B cell response to produce such unusual antibodies have not yet been developed. Another concern is that broad neutralization defined by studies in cultured cells may not translate into broad protection from infection in humans. Inducing cells to produce enough bNAbs to confer protection against primary infection may be essential. For at least some of the flaviviruses, epitope binding can result in either neutralization or more severe pathology, perhaps depending on the absolute number of occupied binding sites, creating a challenge to vaccine safety.



Also see the Antibodies special section, page 1191.

Experimental studies to explore treatments involving the injection of well-characterized bNAbs and that evaluate new vaccination strategies to elicit bNAbs for preventing infection can now build on the emerging science of bNAbs. Several animal studies indicate that infusions of a single bNAb, or combinations of such antibodies, can prevent or control certain viral infections. New technologies to expeditiously isolate specific human antibodies and manufacture them in large quantities have evolved to the point where passive immunization to prevent or treat infection is scalable and is a potentially effective approach to previously refractory infectious diseases or emergent outbreaks. Palivizumab, a licensed antibody product for preventing respiratory syncytial virus infection in high-risk infants, is proof of this concept. For now, the most exciting value of bNAbs may be their utility as probes into the complex host-pathogen interactions that underlie chronic and recurrent viral infections. High-resolution studies of how to shape the evolution of B cell response to elicit bNAbs after vaccination or natural infection will improve the rational design of future vaccine strategies. Ultimately, these efforts will contribute to the prevention and control of some of the most serious and intractable global infectious diseases.

– Julie Louise Gerberding

10.1126/science.1245018

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ECOLOGY

Habitat Histories

The spread of humans around the globe has resulted in the continuing fragmentation of natural habitats. Hence, the science of biodiversity and its conservation increasingly requires an understanding of the dynamics of species persistence in mosaic habitats of varying patch size and history. In an effort to improve predictions of how biodiversity patterns change as humans modify the landscape, Hanski *et al.* have extended the traditional species/area relationship to include a term in the model to account for fragmentation, showing that the traditional model underestimates extinction rates in fragmented habitat. Applied to data for bird populations in the heavily fragmented Brazilian Atlantic forest, the extended model gives improved predictions of local extinctions, especially for species that are better adapted to continuous habitats. In a separate development, Ewers *et al.* have developed an approach that represents the shared history across habitat patches in a similar manner to the way in which phylogenetics represents species relationships. They applied this approach to the biodiversity of forest patches in Brazilian Amazonia and developed a model that uses the history of the formerly connected landscape to predict biodiversity patterns and extinctions in the contemporary fragmented landscape. Their approach provides a mathematical measure of habitat history and facilitates the prediction of the spatial pattern of species that are shared among patches. — AMS

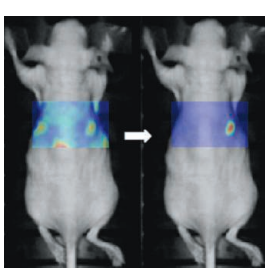
Proc. Natl. Acad. Sci. U.S.A. **110**, 12715 (2013); *Ecol. Lett.* **16**, 10.1111/ele.12160 (2013).



MATERIALS SCIENCE

Beating Fluorescent Background

A challenge for fluorescent imaging of biological samples is that compounds in cells and tissues, such as flavins, autofluoresce. One way to overcome this autofluorescent background is to work in the near-infrared spectral region (wavelengths of 650 to 900 nm). However, even in this region, some background signal is present, so it is desirable to use markers that have longer lifetimes than those of the naturally present molecules (typically tens of nanoseconds). Gu *et al.* describe the use of photoluminescent porous silicon nanoparticles for imaging. The nanoparticles were synthesized by electrochemical etching of the surface of a single-crystal silicon in hydrofluoric acid. This layer was then removed and fractured with ultrasound, and the size-filtered nanoparticles were coated with polyethylene glycol. The luminescent lifetime of the nanoparticles (5 to 13 ms) allowed for time-gated imaging of samples. This approach achieved a greater than 50-fold reduction in background signal in vitro and greater than 20-fold in vivo. The authors used this method to image human ovarian cancer xenografts in a mouse model. — PDS



CREDIT (TOP TO BOTTOM): ALBRECHT DÜRER/WIKIMEDIA COMMONS; LUO GU/UCSD

Nat. Comm. **4**, 2326 (2013).

CHEMISTRY

NO Switching Sides on Copper

For eons, microbes have been shuttling electrons back and forth through nitrogen compounds; some break up N_2 using nitrogenase enzymes, whereas others put it back together via nitrite reductases. In the past century or so, humans have gotten in on the act as well: The Haber process takes N_2 to ammonia (NH_3), whereas at the other end of the cycle, copper catalysts keep noxious nitric oxide (NO) out of exhaust streams by turning it back into N_2. Kwak *et al.* have now uncovered a somewhat unanticipated symmetry between the biochemical and synthetic processes. By using ^{15}N nuclear magnetic resonance and infrared absorption spectroscopy, they gathered compelling evidence for a side-on bonding motif between NO^+ and Cu(I) centers in zeolite catalysts for selective NO reduction. This intermediate resembles the similarly side-bound copper nitrosyl previously observed in a nitrite reductase active site. The authors go on to propose a detailed mechanism for the zeolite reaction by merging their spectroscopic characterization with published kinetic data. — JSY

Angew. Chem. Int. Ed. **52**, 10.1002/anie.201303498 (2013).

NEUROSCIENCE

Axon Bound

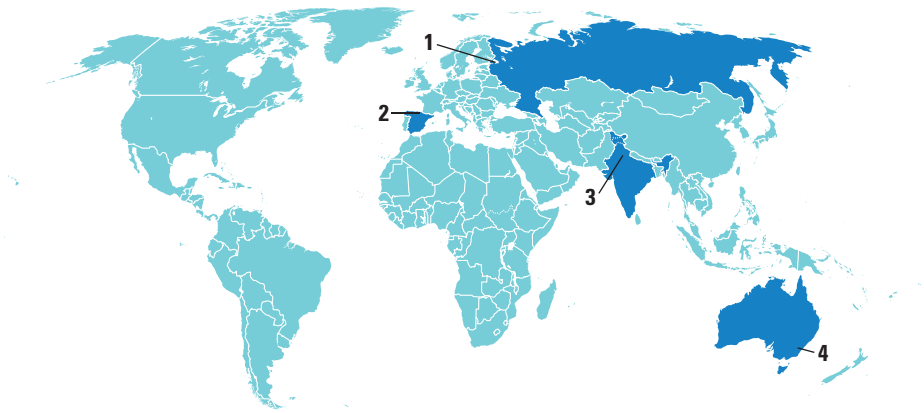
Developing mammalian neurons extend multiple neurites, one of which goes on to form the mature axon. Parker *et al.* have identified distinct and opposite roles for two isoforms of atypical protein kinase C (aPKC). In mammals, the gene *Prkcl* encodes aPKC-λ whereas the gene *Prkcz* encodes aPKC-ζ along with a truncated enzyme PKM-ζ, which lacks the N terminus of aPKC-ζ. In embryonic rat hippocampal neurons, aPKC-ζ was present at the tip of the neurite destined to become the axon, where it associated with polarity complex proteins Par3 and Par6. At the other neurites, Par3 was bound to PKM-ζ, which competed with aPKC-λ for binding to Par3 and inhibited, rather than promoted, axon formation. Thus, competition for binding of the two isoforms, which is then stabilized by feedback, may underlie the symmetry-breaking process that yields the typical neuronal morphology of a long axon and multiple dendrites. — LBR

Proc. Natl. Acad. Sci. U.S.A. **110**, 14450 (2013).

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AROUND THE WORLD



St. Petersburg, Russia **1**

New Curbs on Greenhouse Gases

The G20 group of industrialized nations has agreed to limit emissions of hydrofluorocarbons (HFCs), which are potent greenhouse gases. Production of HFCs, used in refrigerators and air conditioners, has increased in recent years as a substitute for chlorofluorocarbons, an ozone-destroying chemical targeted for eventual elimination under the 1987 Montreal Protocol. The new agreement represents a major concession by India and China, who are big HFC manufacturers and have previously opposed new limits on these organic compounds. The United States and China also signed a bilateral agreement on HFCs.



Cool it. World leaders forged new deal on HFCs.

The new emission limits will rely on "the expertise and institutions of the Montreal Protocol" but will not amend its text—an important clause aimed at preserving the 1987 treaty. "Keeping HFC emissions from increasing to problematic levels is a key component of any sensible overall climate change mitigation strategy," says NASA climate scientist Drew Shindell. The Washington, D.C.–based nonprofit World Resources Institute said the agreements mark "progress … in coming together to curb climate change."

Bilbao, Spain **2**

Neutron Facility's Fate Up in the Air

Plans to build a particle accelerator and neutron source in Spain's Basque Country came to a sudden halt when the governing board of the European Spallation Source (ESS)-Bilbao removed the project's scientific director, Javier Bermejo, and did not renew the contract of ESS-Bilbao's executive director, retiring physicist Joan Bordas. The moves highlight a debate over whether ESS-Bilbao should be a freestanding facility primarily serving Spain, or an R&D test bed for ESS, a $2.4 billion, high-power neutron facility expected to be operational in Lund, Sweden, by 2025.

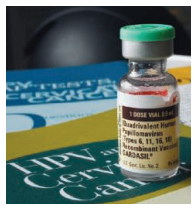
ESS-Bilbao was launched in 2009, after Spain lost a bid to host ESS. In exchange for a 10% ownership of ESS, the Spanish Ministry of Science and Innovation committed $240 million to developing the Bilbao facility to provide components and serve as a technology test bed for the Lund accelerator. But Bermejo had plans for a more ambitious facility that would build its own light-ion linear accelerator and neutron source for local scientists.

What direction the Bilbao facility will take is up in the air. Spain's competitiveness ministry, which now oversees science and innovation, has opened talks with Sweden on redirecting ESS-Bilbao to the original agreement. **http://scim.ag/Spainspall**

New Delhi **3**

Parliament Comes Down Hard On HPV Trial

In a 30 August report, an Indian parliamentary panel excoriated the Seattle-based nonprofit Program for Appropriate Technology in Health (PATH) and the Indian Council of Medical Research (ICMR) for alleged ethical violations in a trial of a vaccine to protect against cervical cancer caused by the human papillomavirus (HPV). In 2009, the groups launched a $3.6 million HPV trial in 24,777 adolescent Indian girls. Several months into the trial, the government pulled the plug after news outlets reported seven deaths, but state investigations found that the deaths were unlikely to be related to the vaccine.



Tried. Merck's Gardasil combats HPV.

The parliamentary report blasts PATH and ICMR for alleged ethical lapses uncovered in 2011 by a panel appointed by the Indian health ministry and also accuses PATH of being a tool of foreign drug companies such as Merck and GlaxoSmithKline, which donated almost $6 million worth of vaccines to the trial.

The fallout from the report could be severe. "After this episode, it will be harder to do clinical trials in India," predicts geneticist Krishnaswamy VijayRaghavan, secretary of the Department of Biotechnology. **http://scim.ag/IndiaHPV**

Canberra **4**

New Government Promises Research Grant Overhaul

A victory for Australia's conservative coalition on 7 September could mean an overhaul of the way certain research grants are distributed. In a press release issued just 2 days before the national election, the incoming government—led by Prime Minister-elect Tony Abbott—promised to scrap Australian Research Council (ARC) grants in research areas it deems unnecessary. In the release, Member of Parliament Jamie Briggs singled out awards in philosophy, religious history, and the intersection of art and climate change, calling them "ridiculous research grants that leave taxpayers scratching their heads."

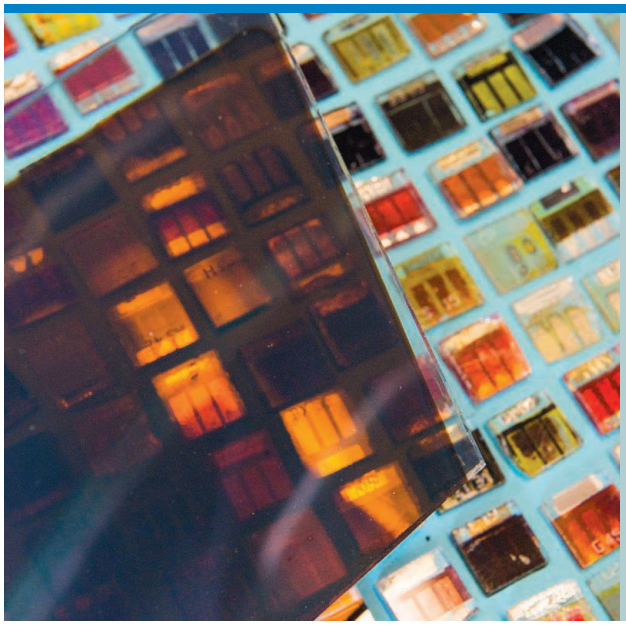


The coalition, Briggs said, won't cut ARC's total budget, and the new government has promised ample funding for dementia and tropical medicine research.

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Seeking a Simpler Solar Cell

An efficient new solar-cell technology uses the same inexpensive manufacturing method as many silicon cells—suggesting that it could be easily adopted by industry. The technology uses a class of materials known as perovskites, in addition to other semiconductors. Physicists had thought that the components of perovskite cells needed to be arranged in an intricate, bubblelike nanostructure to function properly. But the new version of the cells uses flat layers, deposited one on top of another through vapor deposition, a technique already used to manufacture amorphous, thin-film silicon solar cells. The simplified perovskite cells still convert sunlight to electricity at an efficiency of more than 15%, better than the amorphous-silicon cell's 10%, researchers at the University of Oxford in the United Kingdom report this week in *Nature*. "The materials are extremely inexpensive," says Henry Snaith of the Oxford team. Perovskite solar cells could be manufactured for as little as $0.15 per watt, he says, about a quarter of the price of their silicon counterparts.
http://scim.ag/perovcells

Micromanagement of grant selection is not going to go down easy: Scientists are unified in their distaste for government intervention, contends Will J. Grant, an expert on science and policy at Australian National University in Canberra. "It's not for politicians to make a decision" on what types of research are important, says Grant, who notes that the Australian government already sets research priorities for ARC. Once the review process begins, he adds, "the government should stop meddling."

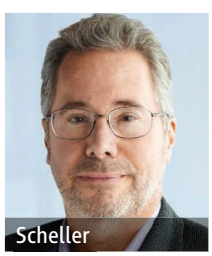
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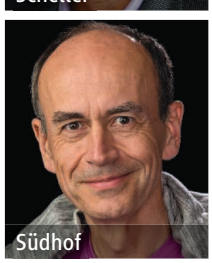
Balzan Prizes to Bacteriology, Quantum Information Processing

The International Balzan Foundation announced its 2013 honorees Monday at a ceremony in Milan. **Alain Aspect**, a physicist at the École Polytechnique in Palaiseau, France, received the prize for Quantum Information Processing and Communication for his experiments to confirm quantum theory and explore quantum entanglement. In the category "Infectious diseases: basic and clinical aspects," bacteriologist **Pascale Cossart** of the Institut Pasteur in Paris was recognized for insights into how pathogenic bacteria interact with and invade host cells. Sociologist **Manuel Castells** of the University of Southern California was also honored for his theories about the social impact of the digital age and the global flow of information. Each of the four Balzan recipients was awarded $800,000, half of it for future research projects.

Lasker Awards Highlight Basic Neuroscience, Cochlear Implants

This year's Lasker Awards, announced Monday, recognized two pioneers in the study of neural signaling and three researchers responsible for modern cochlear implants. **Richard Scheller** of the biotech company Genentech and **Thomas Südhof** of Stanford University in Palo Alto, California, received the Albert Lasker Basic Medical Research Award for their investigation into the cellular mechanisms for releasing neurotransmitters—the brain's chemical messengers. The two worked independently in the late 1980s to identify individual proteins that mediate the process, then developed genetically altered mice lacking these proteins.


Scheller


Südhof

The clinical research award went to **Graeme Clark**, **Ingeborg Hochmair**, and **Blake Wilson** for their work to restore hearing to the deaf. Hochmair and Clark were the first to insert multiple electrodes into the human cochlea to stimulate nerves that respond to different frequencies of sound. Wilson later refined cochlear implants with a strategy known as "continuous interleaved sampling," which enabled them to process speech clearly. Some see the prestigious award, which includes a $250,000 prize for each category, as a hint at future Nobel contenders.
http://scim.ag/Laskers2013

FINDINGS

Reprogramming Cells in Vivo

Researchers have discovered an unexpectedly effective way of "reprogramming" mature mouse cells into an embryolike state, able to become any of the body's cell types: Let the transformation happen in a living animal. In culture dishes, ramping up the expression of just four genes can turn skin and other cells into induced pluripotent stem cells (iPSCs). Researchers in Spain have now developed transgenic mice in which a drug can turn on the four reprogramming genes in all the animals' cells.

The first attempts to induce reprogramming killed the animals within days, the scientists report in *Nature* this week; a lower dose of the drug was not immediately lethal, but the animals developed teratomas, tumors that arise from embryolike cells. Some of the tumors included placental cells—a type of cell that iPSCs and embryonic stem cells can't produce. Finding out why cells reprogrammed in vivo can generate additional cell types could provide new clues to how the process works, and perhaps help it be used in regenerative medicine. **http://scim.ag/invivocells**

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Solar analog. This region around another star resembles our heliosphere, which Voyager 1 may have left.

PLANETARY SCIENCE

It's Official—Voyager Has Left the Solar System

After 36 years of hurtling toward the edge of the solar system, the Voyager 1 spacecraft—its sensors failing, its energy running low—has crossed into the abyss of interstellar space. At least, that is now the consensus view of Voyager mission team leaders. This week, four team members are publishing new data from Voyager 1 in *Science* that the team deems conclusive: Its spacecraft has passed out of the heliosphere, the bubble inflated by the sun's wind of charged particles. Voyager, now six times farther from Earth than the orbit of Neptune, is where nothing from Earth has gone before.

The much-anticipated departure of the storied probe, which visited Jupiter and Saturn before heading out of the solar system, may sound like familiar news. Over the past year, there have been reports of its leaving, of its not quite leaving, of its being in a new, special place. There's a reason for the mixed signals. The space physicists' edge of the solar system "is not your usual planetary environment at all," says heliophysicist George Gloeckler, a Voyager team member since the 1960s. Even modern computer simulations could give the researchers no warning of the confusing weirdness Voyager 1 has encountered.

What's more, the instrument capable of detecting the clearest sign that Voyager had crossed the heliopause—the outer boundary of the heliosphere—failed long ago. So there has been plenty of room for interpretation and disagreement, with some members of the team and outside investigators offering interpretations at odds with the official word from the five Voyager instrument principal investigators, the Science Steering Group (SSG).

Online
sciencemag.org
Podcast interview with author Richard A. Kerr (http://scim.ag/pod_6151).

The arguments began in August 2012, when the counts of energetic charged particles, or cosmic rays, showering the spacecraft changed abruptly. On 25 August, a Voyager 1 instrument recorded a sharp drop in cosmic rays that are produced inside the heliosphere, a drop that soon continued to near zero. Another instrument recorded a simultaneous increase in cosmic rays produced outside the heliosphere far out in the galaxy.

"I thought we had crossed into interstellar space," says J. Randy Jokipii, a 50-year veteran of space physics theory at the University of Arizona in Tucson and a longtime Voyager guest investigator. Edward Stone of NASA's Jet Propulsion Laboratory in Pasadena, California, was more cautious. He is principal investigator of Voyager's Cosmic Ray Subsystem experiment, so he has a special affinity for last year's surprising data. But he has also been the mission's project scientist from the start—and the SSG's consensus-maker. "We knew we were in a new region close to the boundary" with interstellar space, he says. But had Voyager really left, he wondered? Or was this just an unexpected region of the outermost heliosphere?

The answer would be a downer. Astronomers had expected that the direction of the magnetic field that pervades all space would switch at the heliopause, where the fields carried by the charged particles of the solar wind give way to those of interstellar medium. But according to the lengthy calibration and analysis of the Voyager 1 magnetometer data completed in early December, "there was no change in direction" the previous August, Stone says, so "we were cautious to not claim a crossing. We all concluded we didn't have definitive evidence of crossing into interstellar space."

At December's American Geophysical Union (AGU) meeting in San Francisco, Stone played it cool. Instead of calling a full-blown press conference, he explained to reporters one at a time in a "media availability" that as of August, Voyager 1 was still inside the heliosphere. Things had clearly changed, he said; Voyager 1 had entered an unexpected heliospheric region dubbed the "magnetic highway." There, magnetic field lines somehow connected the heliosphere's interior with interstellar space, allowing energetic particles like cosmic rays to leak out and in. But Voyager hadn't left, because the magnetic field direction hadn't changed.

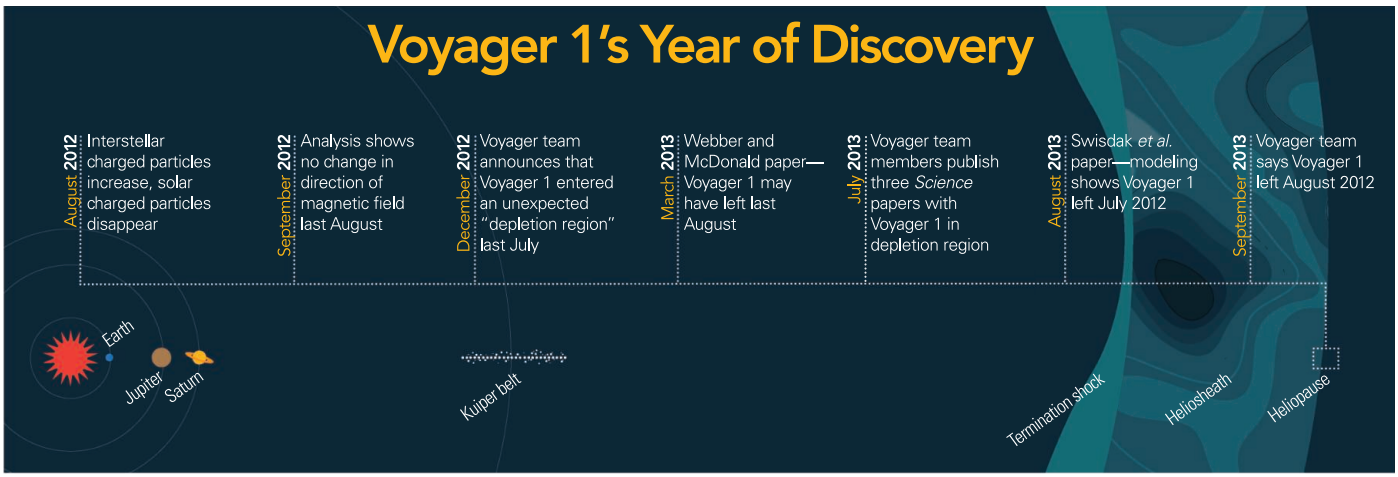
Voyager principal investigators followed Stone's lead in three papers submitted to *Science* early this year and published 12 July, which had Voyager 1 entering a "depletion region," jargon for the magnetic highway. But in Jokipii's view, "everybody punted. There was no consensus of what was going on."

Not everyone followed the official line, however. "Voyager 1 has left the solar system, sudden changes in cosmic rays indicate" was

CREDIT: NASA AND THE HUBBLE HERITAGE TEAM (STSCI/AURA)

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Gone or not? In the past year, Voyager 1 sent back data that led to conflicting interpretations. Had it left the heliosphere in August 2012? The latest data suggest that it did.

CREDIT: G. GRULLÓN/*SCIENCE*

the headline of a press release accompanying a paper on the August cosmic ray measurements, accepted on 20 March at AGU's *Geophysical Research Letters*. Within hours, AGU changed the headline to "Voyager 1 has entered a new region of space." The paper's first author and Voyager team member William Webber privately agreed with the initial headline. "We thought it was at the crossing, but in deference to the team, we didn't push that aspect of it" in the paper, says the professor emeritus at New Mexico State University in Las Cruces.

Six months later, a group of Voyager outsiders again placed the spacecraft in interstellar space. "We think we are outside the heliopause," says space physicist Marc Swisdak of the University of Maryland, College Park.

As they reported in the 1 September *Astrophysical Journal Letters*, Swisdak and his colleagues used the most detailed model yet to simulate how particles and fields behave at the heliopause. "The boundary is very different than we thought," he says. "The very nature of the heliopause may come into question." Their picture of the heliopause accounts for both the changing cosmic ray counts and the unchanged magnetic field direction, he says. In their model, the two magnetic fields, inside and outside the solar system, line up and connect to each other.

Now comes the latest official word from the Voyager team, and the verdict is that the 25 August 2012 changes did signal an exit from the heliosphere. "That is the collective point of view" of the Voyager team, Stone says. What prompted the change of heart was observations by Voyager 1's plasma wave instrument, which measures oscillations in the plasma, the soup of low-energy charged and neutral particles pervading space.

A jump in the density of plasma "is the way the heliopause has been defined for years," says Donald Gurnett of the University of Iowa in Iowa City, who is the principal investigator of the plasma wave instrument. An instrument that could directly measure the plasma density broke shortly after the spacecraft passed Saturn. In the debate over the heliopause, "the key thing missing was plasma," Gurnett says. But Gurnett's instrument can be used to infer plasma density indirectly, at least when the sun sends a blast out Voyager's way, triggering distinctive oscillations in the plasma.

This past 9 April, Voyager 1 recorded the sudden onset of plasma oscillations at a frequency of 3.1 kilohertz following a solar outburst. "When we saw that, it took us 10 seconds to say we had gone through the heliopause," Gurnett says. That frequency implied a plasma density 80 times larger than ever seen inside the heliosphere and close to the density that astronomers were expecting in interstellar space. As Gurnett and three other Voyager team members report online in *Science* this week (http://scim.ag/DGurnett), they could infer a departure date of 25 August 2012 by extrapolating back through a weaker, recently recognized oscillation episode of lower frequency last October. "Plasma trumped magnetic field in this case," Gurnett says.

Gurnett's "conclusions are remarkable and probably correct," Jokipii says. "Now we have three detectors all consistent in suggesting strongly we're in the interstellar medium." And for most researchers in and out of the Voyager team, that is enough; Voyager 1 has left.

That conclusion is far from unanimous, however. "I don't think it's a certainty Voyager is outside now," says space physicist David McComas of the Southwest Research Institute in San Antonio, Texas. "It may well have crossed," he says, but without a magnetic field direction change, "I don't know what to make of it."

Heliophysicist Gloeckler and heliosphere theorist Lennard Fisk, both research professors at the University of Michigan, Ann Arbor, simply reject the Voyager team's interpretation. "We have not crossed the heliopause," Gloeckler says. "We're way out there, by far a minority, but we can explain every Voyager result in a pretty natural way." The jump in plasma density is merely the solar wind piling up just inside the heliopause, he says.

Time should tell. The radioisotope thermoelectric generators powering Voyager 1 and Voyager 2—which is cruising a few years behind its twin—have been running down since before launch. Starting in 2020, Voyager 1's instruments must share power by rotating on and off. By 2025, its last instrument will be shut down for good. But that could still be time enough for a direction change in the magnetic field to turn up, or not. Or Voyager 2's still-intact plasma instrument could prove Gloeckler and Fisk right. At only $5 million a year in operating costs for both spacecraft, NASA isn't likely to bring this interstellar mission to a premature end.

And Voyager team leaders are preparing for an even longer run. "I never knew I was signing up for a lifetime," says Voyager principal investigator Stamatios Krimigis of the Applied Physics Laboratory in Laurel, Maryland. "It's a marvelous mission, but I'm doing succession planning."

–RICHARD A. KERR

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CLIMATE SCIENCE

Researchers Wary as DOE Bids to Build Sixth U.S. Climate Model

Scientists who use computer simulations to understand Earth's climate, past and future, may soon get a potent new tool. The U.S. Department of Energy (DOE), a powerhouse of supercomputing, is planning to create its own computer climate model, the sixth in the U.S. modeling toolbox. But while some climate scientists applaud the nascent project, which promises more detailed simulations than existing models, others worry that it could drain talent from existing collaborations.

Modeler James Hurrell, director of the National Center for Atmospheric Research (NCAR) in Boulder, Colorado, which runs one of the major existing U.S. climate models, acknowledges the concerns. But he says, "There's a real need for high-resolution models that can run efficiently on the next generation of supercomputers—I choose not to view this as a threat."

Earth simulators built from thousands of lines of computer code have become central to climate science. Many industrialized nations have funded the development of one or more models, which seek to forecast how rising carbon dioxide levels in the atmosphere will affect an array of factors, including air and ocean temperatures, ocean currents, and polar ice. Existing models tend to do best when focused on the big, global picture. Increasingly, however, scientists and policymakers are keen to have higher resolution models able to zoom in on features smaller than 100 square kilometers, such as ocean eddies, storms, or mountains. Tests suggest that adding these details—and some supercomputing firepower—can greatly improve a model's forecasts.

The five existing U.S. modeling efforts focus on various scales and issues (see box). One of the best known is NCAR's Community Earth System Model (CESM), created by the National Science Foundation, DOE, and hundreds of academic scientists. DOE says its new model, as yet unnamed, would be a distinct, higher resolution version of CESM. It would aim to answer questions such as how global warming might affect biofuel crops or water supplies for power plants. "With a combination of extensive modeling expertise and access to the world's fastest computers, DOE national laboratories are uniquely positioned to spearhead such an effort," the agency wrote in response to questions from *Science*.

The project would involve seven DOE labs, officials say, and would not require new spending. They expect to launch the effort within 4 months, but "only after a positive outcome to the peer review process and DOE approval." DOE will share its computer code with scientists running CESM and other programs, they add, which might allow those efforts to achieve higher resolutions as well.

That strategy sounds promising to some. It might allow NCAR, for instance, to focus on other problems, Hurrell says. These could include better simulating regional cycles like El Niño or the climatic role of aerosol particles. And it could give the world's modeling community another test bed for fine-tuning projections that feed into policymaking processes.

DOE's fresh start could also result in a nimbler team that has more freedom to pursue riskier approaches. The CESM team includes a number of researchers who left NCAR as a result of budget woes and are now at DOE (*Science*, 22 August 2008, p. 1032). Some have felt stifled by the collaboration's bureaucracy. All changes to the model must be approved through a rigorous vetting process, for example, sometimes leaving new ideas on the cutting room floor. "CESM tends to gravitate towards what works well," says climate modeler Chris Bretherton of the University of Washington, Seattle. DOE's modelers will have the freedom of a clean slate.

Still, others note that last year, a National Research Council report called for a more "coordinated" and "integrated" U.S. modeling program—not an additional simulation. (It also called for higher resolution modeling.) And although DOE says it has no plans to reduce its financial support for CESM, $6.2 million this year, some fear the new model could divert DOE scientists from existing collaborations. "It's great there's a new initiative," says modeler Inez Fung of DOE's Lawrence Berkeley National Laboratory and the University of California, Berkeley. "But all the modeling efforts are very short-handed. More brains working on one set of code would be better than working separately."

Critics wonder, for instance, how the new effort could affect DOE researchers such as Philip Rasch of the Pacific Northwest National Laboratory in Richland, Washington. A former NCAR modeler, he's remained a vital part of CESM: "It's as if he's still here, frankly," says NCAR modeler Richard Neale. If DOE moves ahead, however, Rasch could be assigned to work on the new model. "Whether or not [he] can spend his time the way he has over the last few years is still an open question," Hurrell acknowledges. (Rasch and other DOE scientists declined interview requests.)

DOE's initiative may also spur policymakers in Washington to ask an uncomfortable question: Does the United States really need six climate models? Last year, the White House Office of Management and Budget quizzed agencies on the plethora of models, and Republicans on the House of Representatives science committee have decried what they see as money wasted on climate science. DOE's effort may represent yet another target. **–ELI KINTISCH**



MAJOR U.S. CLIMATE MODELS

Name or institution	Funder	Notes
Community Earth System Model/NCAR	NSF-DOE	Most extensive global modeling effort; couples atmosphere, ocean, and land
Geophysical Fluid Dynamics Laboratory	NOAA	Major model includes Princeton University contributions
National Centers For Environmental Prediction	NOAA	Focus on short- to medium-term weather prediction
Goddard Institute for Space Studies	NASA	Emphasis on global and regional climate sensitivity
Goddard Earth Observing System	NASA	Earth system model informed by space observations
Proposed DOE Model	*DOE*	*Would focus on higher resolution modeling*

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SPACE SCIENCE

Novel Craft Sets Out to Probe the Mysteries of Moondust

Much is riding on a lunar science mission that NASA launched last week from its Wallops Flight Facility on the Virginia shore. And it isn't just lunar science.

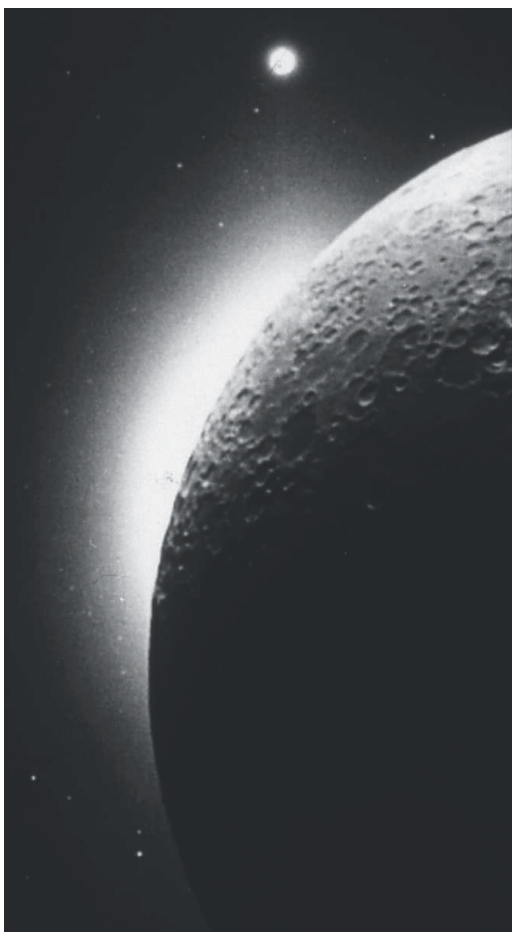
The primary goal of the Lunar Atmosphere and Dust Environment Explorer, or LADEE (pronounced "laddie"), is to learn more about the moon's thin atmosphere, which is still mysterious 4 decades after humans last landed on the moon. But the launch will also test a number of new concepts and technologies that could help future space missions. "It's got a lot of firsts to it," says Richard Elphic, project scientist for LADEE at NASA's Ames Research Center in Moffett Field, California.

For one, LADEE is the first mission to be blasted into space atop a Minotaur V rocket, a newly designed commercial launch vehicle that incorporates parts from a retired intercontinental ballistic missile—cheaper than building them from scratch. Another first is that LADEE was assembled from modules whose designs could be reused to build future spacecraft. It will also give NASA its first chance to test a new laser-based system that could significantly boost data downloads from observational satellites.

LADEE was conceived as part of the Bush administration's Constellation program to return astronauts to the moon. The Obama White House canceled Constellation in 2010, but LADEE survived "because the science that LADEE will be doing was still relevant," Elphic says. "We have questions about the moon that have gone unanswered for years."

One of those questions stems from something astronauts on several Apollo missions saw on the moon decades ago: a surprising predawn glow on the lunar horizon, similar to the glow seen before sunrise on Earth, as sunlight is scattered by moisture and dust. Astronomers have speculated that the "lunar horizon glow" could be the result of light scattering off a cloud of dust hovering over the lunar surface—perhaps lofted by static electric charges on the grains. The dust cloud should allow LADEE, orbiting as low as 20 kilometers above the lunar surface, to sample the same dust Apollo astronauts encountered at the surface, where they reported returning from moonwalks with their suits covered in fine powder that smelled like gunpowder. The nature of the dust, and exactly what holds it aloft in the near absence of an Earthlike atmosphere, are among the questions researchers want answered.

CREDIT: NASA



Stray rays. Horizon glow spotted by the Clementine lunar orbiter gives evidence of sunlit moondust.

LADEE's Lunar Dust Experiment (LDEX) will capture and ionize the dust particles, and detectors will collect the resulting electrons and ions. From the two signals, "we will be able to tell the mass and speed of the particles, as well as the charge they carry," says Mihály Horányi, principal investigator of LDEX and a physicist at the University of Colorado, Boulder.

Two other instruments round off LADEE's scientific suite: the Ultraviolet and Visible Light Spectrometer, which will help determine the composition of the extremely rarefied lunar atmosphere, and the Neutral Mass Spectrometer, which will measure how the atmosphere varies as the moon moves through space. (The lunar atmosphere, a near-vacuum by Earth standards, consists largely of atoms outgassed by radioactive rocks or blown in on the solar wind.)

Characterizing the lunar atmosphere and its dust will also help astronomers interpret observations of planets in the solar system and beyond. "A lot of our knowledge about surfaces of planets comes through remote sensing," Horányi says. "If the surface properties are dictated by a layer of dust a few microns thick, we need to know more about the dust."

LADEE will send back its findings via a new laser communication system that could radically increase the amount of data that researchers can harvest from space missions. Now, nearly all satellites communicate with one another and with Earth by radio. LADEE will beam down its data through light pulses that will give it six times the bandwidth of the Lunar Reconnaissance Orbiter's (LRO's) radio transmissions, while using one-fourth the power, says NASA's Don Boroson, principal investigator for the LADEE's Lunar Laser Communication Demonstration. LADEE's data-receiving and transmission system also weighs about half as much as LRO's.

"Right now, space scientists often feel that they have to leave data on the table—they have to pick and choose how many images to download for a target, for example," Boroson says. With laser-based communication, he says, "scientists will have access to far more raw data from any mission."

LADEE's novel design could also set a pattern for future missions. The spacecraft was assembled from modules whose designs can be reused in the future—for example, an avionics module and an instrumentation module. "More than 80% of the cost of building a spacecraft is not in materials but in nonrecurring engineering," Elphic explains. "If you can go to designs that already exist for different modules, you are way ahead." So, he says, the work done to build LADEE could lower the cost of missions to come.

It will be a month before researchers start getting any data from LADEE. That's because the spacecraft is taking a slow but thrifty route to the moon. The launch last week put LADEE in a large eccentric orbit around Earth. Over the next 3 weeks, it will loop around Earth three times, its orbit widening with each loop. By the end of the third loop, it will be close enough to the moon for a small nudge from LADEE's motors to propel it into lunar orbit.

–YUDHIJIT BHATTACHARJEE

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Handle with care. Genome testing could enhance newborn screening, but it raises ethical issues.

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GENOMICS

Researchers to Explore Promise, Risks Of Sequencing Newborns' DNA

Last week, U.S. human geneticists moved into perhaps their most sensitive ethical territory yet: whether it might someday make sense to sequence every newborn's genome so the information can be used in the child's medical care. That prospect raises a host of questions about what parents should be told about their baby's genes. Should they know, for example, that their child is at high risk for cancer later in life?

"We can see the potential value of looking at an infant's genome to examine all of the genes or perhaps a particularly informative subset of them," explained Alan Guttmacher, director of the National Institute of Child Health and Human Development (NICHD), in rolling out a $25 million, 5-year federal research program to explore these issues. Genome testing could supplement the decades-old state screening programs that take a drop of blood from nearly every newborn's heel and test it for biochemical markers for several dozen rare disorders. Diagnosing a child at birth can help prevent irreversible damage, as in phenylketonuria, a metabolic disorder that can be controlled with diet.

Screening often turns up false positives, however, which genetic tests might help avoid. And genome sequencing could potentially look for all 7000 or so diseases caused by defects in single genes. Ever-cheaper sequencing is making this more feasible: An entire genome now costs $5000, and decoding just protein-coding DNA—the "exome"—can be done for $1000, compared with several hundred dollars to test for a single genetic mutation.

But genome sequencing, unlike the current newborn screening tests, could potentially reveal many more unexpected genetic risks, some for untreatable diseases. Which of these results should be divulged is already controversial. Sparks are still flying over a report in March from the American College of Medical Genetics and Genomics (ACMG) that listed 57 disease risk mutations that should be reported to a patient (or to a child's parents) when his or her genome is sequenced as part of routine clinical care (*Science*, 29 March, p. 1507).

To explore how sequence data from newborns might be used in medical care, as well as the related ethical, legal, and social issues, NICHD and the National Human Genome Research Institute are funding four pilot projects. All will examine whether genomic information can improve the accuracy of newborn screening tests, but they differ in which additional genes they will test and what results they will offer parents.

One group will use sequencing for very sick newborns to help diagnose their illness quickly. Lead investigator Stephen Kingsmore at Children's Mercy Hospital in Kansas City, Missouri, wants to halve the time for his current 50-hour test, which he has used to diagnose genetic disorders in up to 50% of infants in his hospital's neonatal intensive care unit. The test homes in on a subset of genes that may explain the baby's symptoms. While his group may ask parents if they're interested in unrelated genetic results, the focus is on "a critically ill baby and a distressed family who want answers," Kingsmore says.

A team at the University of North Carolina is studying how to return results to the poor and others who might not be familiar with genomics. But it is also dividing genetic findings into three categories—mutations that should always be reported; those that parents can choose to receive, which might include risk genes for adult cancers; and a third set that should not be disclosed. That last set includes risk genes for untreatable adult-onset diseases such as Alzheimer's.

A team at Brigham and Women's Hospital in Boston and Boston Children's Hospital hopes to learn how doctors and parents will use genomic information. "We're trying to imagine a world where you have this information available, whether you're a sick child or healthy child. How will it change the way doctors care for children?" asks co-principal investigator Robert Green of Brigham and Women's, a lead author of the ACMG report on unexpected findings.

Genome sequencing might never replace existing newborn screening because of its costs and the complexity, says ethicist Jeffrey Botkin of the University of Utah in Salt Lake City. But he and others say it is important to explore these issues because wealthy, well-informed parents will soon be able to mail a sample of their baby's DNA to a company to have it sequenced—regardless of whether medical experts think that's a good idea. "There's an appetite for this. It will be filled either within the medical establishment or outside of it," Green says. **–JOCELYN KAISER**

Studies on Benefits and Risks of Newborn Genomic Sequencing

Institution	Number of infant genomes	Objectives include
Brigham and Women's, Boston Children's hospitals, Boston	120 sick, 120 healthy	Study how parents and doctors use genomic data
Children's Mercy Hospital, Kansas City, Missouri	500 sick	Diagnose genetic disorders within 24 hours
University of California, San Francisco	~1250 sick, ~200 healthy	Assess parent interest in drug metabolism genes
University of North Carolina, Chapel Hill	200 sick, 200 healthy	Study how to share results with multicultural families

New ground. Four projects funded at a total of $25 million over 5 years will look at how genome testing could improve newborn screening and other questions.

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Alarm Over Autism Test

A hypothesis that maternal antibodies can impair fetal brains stirred plenty of doubts—and that was before the researchers set out to turn it into a test for predicting autism

JACKIE MURPHY DIDN'T WORRY THAT HER son Fintan was a late talker, at least at first. Her other two children had been slow to say their first words, so it was only when the former California nurse noticed that her 20-month-old wasn't responding to his name, or even reacting to loud noises, that she became concerned. "One day, I dropped a toy xylophone behind him and he didn't even flinch," she says. "That's when I knew something was wrong."

Fintan didn't have a hearing problem—he had autism, his mom finally learned after more than 6 months of searching for a diagnosis. A few months later, Murphy enrolled Fintan in the Autism Phenome Project at the MIND Institute at the University of California (UC), Davis, a long-term assessment of children, as many as 1800, aimed at teasing out subtypes of the complex disorder. Murphy also became a research subject, donating a blood sample.

One of the project's researchers, Melissa Bauman, soon informed Murphy that her blood had tested positive for antibodies that react to fetal brain proteins. Bauman asked her to donate more blood for studies exploring the provocative idea that some of Murphy's antibodies had slipped through the placenta and into Fintan's developing brain, affecting its maturation. At that point, Murphy says, she and her husband made a big decision: Fearing that the immune proteins in her blood would harm another baby, they decided that she would not again get pregnant.

Many more women could face a similarly difficult choice. In July, immunologist Judy Van de Water and her team at UC Davis, which includes Bauman and Daniel Braunschweig, bolstered the hypothesis that maternal antibodies cause some autism with two studies, including one showing autismlike symptoms in monkeys injected with such antibodies. And women may soon be able to check whether they have the suspect antibodies: California company Pediatric Bioscience announced that it is moving forward with a new diagnostic test, based on patented antibody screening techniques licensed from Van de Water and UC Davis.

According to a press release issued by the company at the time, a positive result on the test, estimated to cost roughly $800 and be ready in about 18 months, could tell a woman that she has a "99 percent likelihood" of having a child with autism if she

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Looking for answers. Immunologist Judy Van de Water (*far right*) suspects that antibodies carried by Jackie Murphy (*middle*) may have contributed to the autism of her son Fintan (*far left*; Murphy's son Tiarnan, in green, does not have autism).

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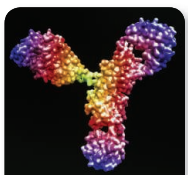
became pregnant. It could also tell parents if the child they just had is likely to develop autism, especially if there are already signs of a developmental delay. Such a scenario, says company President Jan D'Alvise, would let parents enroll a child in early interventional therapies, even before symptoms develop. Already, "people are e-mailing me, saying, I would like to get the test, where can I get the test," Van de Water says.

Pediatric Bioscience's announcement, however, has alarmed many autism researchers. "This is very, very premature—this research has come out of one group, and basically one study. I'm amazed that they're going ahead at this point and trying to commercialize a test," says autism researcher George Anderson of Yale University. He and others say that Van de Water's data are too preliminary, and her statistics too weak, to support such clinical uses. They are skeptical of the mechanism she has proposed for how maternal antibodies could damage the fetal brain. And before any antibody test for autism is launched, they say, her results need to be extensively replicated. "This whole thing could be a house of cards," warns Thomas Wassink, a geneticist at the University of Iowa in Iowa City who studies autism.

Perhaps the most controversial aspect of the proposed test is that some already pregnant women might decide to abort their babies on the strength of the results. Van de Water emphasizes that Pediatric Bioscience plans to limit the "intended use" of the maternal antibody test to women who are not currently pregnant. The company is planning to develop and conduct the test exclusively, she says, thus allowing for control over its use and proper counseling for families. Van de Water is also seeking validation of her group's initial studies, with three large prospective trials under way, but she nonetheless feels compelled to push ahead with Pediatric Bioscience on the test. "The community in autism is a very frustrated group of people. They feel like we've done a lot of research but none of that is impacting our lives right now. … If you wait until I have thousands of samples that's kind of late," she says.

Controversial origins

This isn't the first time purported connections between the immune system and autism have ignited controversy. In 1998, the British physician Andrew Wakefield claimed that eight of 12 children with neurodevelopmental delays had experienced a sudden onset of autism symptoms after receiving the measles, mumps, and rubella (MMR) vaccine. In a press conference held in coordination with the publication of a study in *The Lancet*, he hypothesized that the triple dose of vaccines could trigger an immune reaction that damages the brain. The study was later retracted, Wakefield was stripped of his medical license for falsifying the medical histories of the children, and more than a dozen epidemiological studies have failed to find any connection between childhood vaccines and autism. But the link has yet to be dissolved in the public imagination, says Emanuel DiCicco-Bloom, a child neurologist and neuroscientist at Rutgers University in Piscataway, New Jersey.



Also see the Antibodies special section, page 1191.

That history puts an extra burden of responsibility on researchers considering immune hypotheses for autism. It has also made exploring such hypotheses more difficult, notes Karoly Mirnics of Vanderbilt University in Nashville, a neuroscientist who studies immune changes in autism, schizophrenia, and other mental disorders. "Ten years back, you could not get funding" for this type of research, he says. "You could not publish it. You were sort of considered to be on the fringes of science."

> **The community in autism is a very frustrated group of people. They feel like we've done a lot of research but none of that is impacting our lives right now. … If you wait until I have thousands of samples that's kind of late.**
>
> **—JUDY VAN DE WATER, UC DAVIS**

One place where researchers interested in immune connections to autism have found support is the MIND Institute, which was founded in 1998 by influential California families who had a "big interest" in the MMR hypothesis, Van de Water says. Vaccine research, however, is no longer a focus at the institute, according to Van de Water, and her work does not directly involve vaccines.

An emerging body of evidence unrelated to childhood vaccines suggests that a mother's immune system may play a role in offspring developing autism, says Paul Patterson, a biologist at the California Institute of Technology in Pasadena who studies interactions between the nervous and immune systems. For example, epidemiological studies have shown that several types of infection during pregnancy can increase the risk that a child will develop schizophrenia or autism, he says. Families with autoimmune disorders such as rheumatoid arthritis and celiac disease are also more likely to have children with the disorder. Patterson's own lab has conducted animal studies showing that inflammatory molecules produced by a pregnant mother in response to an infection such as the flu can affect fetal brain development. "It's a very reasonable hypothesis to be out there testing because of the epidemiologic connection between learning disabilities and mothers with a variety of autoimmune diseases," says Daniel Geschwind, director of the Center for Autism Research and Treatment at UC Los Angeles. "It looks like there's some epidemiologic signal there—the question is, is that a causal relationship?"

Van de Water's interest in maternal antibodies was sparked by a 2003 study by researchers at the University of Oxford, which focused on one 38-year-old mother. The woman had two relatively normal children—a girl with high-functioning autism spectrum disorder (ASD) and a typically developing boy. However, her third child, a 6-year-old boy, had appeared fairly normal until about 18 months and then quickly regressed to severe autism, losing all language. When the researchers extracted serum from the mother, they found that some of her antibodies bound to neurons taken from a developing mouse brain, and they suggested that the antibodies could have triggered her son's condition.

Other researchers have pursued the maternal antibody hypothesis over the past decade, but Van de Water's team has taken it the farthest, Patterson says. In 2008, the group expanded on the Oxford study by extracting serum from 61 mothers of children with autism. About 11% of the

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mothers carried antibodies that reacted strongly to a group of unidentified brain proteins in human fetal brain tissue, and the level of reactivity corresponded with the severity of the child's autism symptoms. None of the 102 control mothers showed the same pattern of reactions.

Van de Water's latest work, published in the journal *Translational Psychiatry*, expands the sample still further, to 246 mothers of children with autism. She and her colleagues found that 23% carried antibodies that react to fetal brain tissue, compared with only 1% of 149 mothers who have typically developing children. This time the team pinpointed seven specific proteins that the antibodies target, including ones linked to the proliferation of neurons, neural migration during development, and neural branching (see diagram). "Each works at some stage in the development of a neuron," Van de Water says.

It's not clear why a woman would generate such reactive antibodies. "We may never know," Van de Water says. Some women may be genetically predisposed to produce the antibodies in response to an immune insult such as an infection, or even a vaccine, she suggests. Although that's pure speculation for now, Murphy, who has become a close friend of Van de Water, is already persuaded that a vaccine she received contributed to Fintan's autism. "He's the only one I got vaccinated with the flu shot during pregnancy," she says.

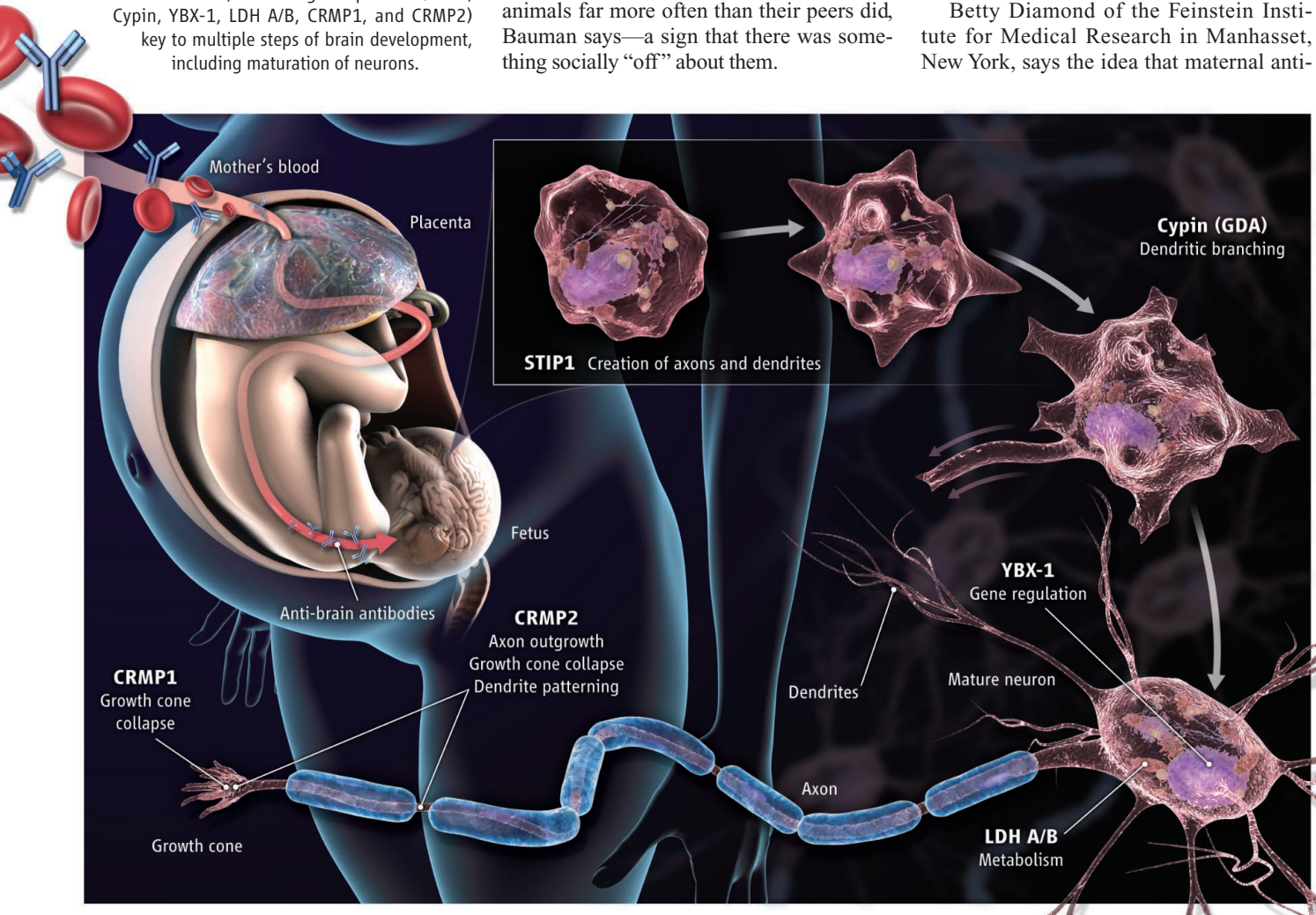
In her other new study, Van de Water teamed up with Bauman and neuroscientist David Amaral, director of the MIND Institute, to link the autism-associated antibodies to symptoms. The team reported that when pregnant rhesus monkeys were injected with these human maternal antibodies, their infants developed behavioral and brain development problems. The researchers say the symptoms resemble some of those seen in people with autism. For example, the young monkeys whose fetal brains had been exposed to the antibodies directly approached unknown animals far more often than their peers did, Bauman says—a sign that there was something socially "off" about them.

Strong reactions

Van de Water's latest work is "an important step that lots of people have been waiting to see," Patterson says. If she's right, "we're at least doubling" the number of autism cases we can explain, adds Andrew Zimmerman, a pediatric neurologist at the Kennedy Krieger Institute in Baltimore, Maryland. Now, only 15% to 20% of autism cases can be traced to a specific cause, he says—primarily genetic mutations.

But other reactions range from skeptical to sharply negative. Zimmerman himself says that absent replication of Van de Water's clinical results in much larger groups of women, "it isn't clear yet what the [autism] risk to a particular pregnancy is if a mother has the antibodies." He and others also question the maternal antibody hypothesis itself. For example, it assumes that the so-called blood brain barrier, which normally protects the brain from molecules such as antibodies, is permeable enough in fetuses for antibodies to enter and for them to do damage—a fact that has yet to be rigorously established, DiCicco-Bloom says.

Betty Diamond of the Feinstein Institute for Medical Research in Manhasset, New York, says the idea that maternal anti-



Inflammatory hypothesis. Van de Water and colleagues propose that antibodies in a mother's bloodstream travel through the placenta and cross the fetal blood brain barrier, interfering with proteins (STIP1, Cypin, YBX-1, LDH A/B, CRMP1, and CRMP2) key to multiple steps of brain development, including maturation of neurons.

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bodies directly cause autism in some cases is "plausible." In her own lab, Diamond has demonstrated that pregnant mice injected with antibodies made by women with lupus that target DNA-associated proteins and certain cellular receptors on the surface of neurons bear offspring with abnormal brain structures and cognitive problems. And just last month, Diamond published a study of blood from 2700 mothers, which found that roughly one in 10 mothers of children with autism carried what her team calls "anti-brain" antibodies—a ratio roughly four times higher than controls. Preliminary studies suggest that the antibodies targeted proteins different from those that Van de Water has identified, however, and Diamond herself is not ready to claim that these antibodies actually cause autism.

Indeed, Van de Water's dramatic claim that maternal antibodies could play a role in a quarter of all autism cases disturbs many researchers. Because the serum of the tested mothers displayed varying patterns of reactivity to the seven fetal brain proteins—some binding to just one and others to up to five—the researchers added up many different "specific combinations" of reactivity to get their figure of 23%. No specific pattern of reactivity was observed in more than 7% of the mothers of autistic children that they tested, notes Steven Goodman, a biostatistician at Stanford University in Palo Alto. He described the approach as a form of data dredging—sifting data for the largest effects—which at best exaggerates predictiveness, and at worst finds patterns that aren't real.

Ultimately, DiCicco-Bloom says, Van de Water's studies will need to be replicated in thousands of women from different backgrounds to establish whether the maternal antibodies have any predictive value. That should be fairly easy to do, now that the fetal brain proteins targeted by the antibodies have been identified, notes epidemiologist Ian Lipkin, of Columbia University, principal investigator of the Autism Birth Cohort, a large Norwegian study of more than 100,000 children.

Van de Water agrees that her new work needs to be replicated by independent groups. She adds that she is involved in three large prospective studies now in progress at UC Davis, all funded by the National Institute of Environmental Health Sciences. "I didn't want people to get the impression that this was final," she says of her most recent work. "This was really a discovery paper, and not a clinical validation."

Testy questions

Then why, critics ask, is Pediatric Bioscience already trumpeting a test? Van de Water argues that developing the test in parallel with the research means it will be available sooner for doctors to order. "We'll also know if it's not going to work more quickly," she says. She adds that she is facing competition from other groups, such as Diamond's lab.

Anderson is not persuaded. "They're overstating what they have, and then they're proceeding too quickly," he says. "You don't need to commercialize something to make it available as a research tool."

The researcher's corporate ties add to the unease. "She has a patent, and you could perceive a conflict of interest there," DiCicco-Bloom says. Van de Water emphasizes that her relationship with Pediatric Bioscience has been thoroughly vetted by UC Davis, which allows her to split a 30% share of whatever royalties the company pays to the university for use of the patent with other investigators on the team. As chief scientific adviser to Pediatric Bioscience, Van de Water cannot perform the clinical validation studies herself because that would violate the UC Davis policies guarding against conflicts of interest; she is also prohibited by the university from accepting free or discounted stock in the company, she adds.

> **"This is very, very premature. … I'm amazed that they're going ahead at this point and trying to commercialize a test."**
>
> **—GEORGE ANDERSON, YALE UNIVERSITY**

Financial considerations aside, the key to any medical diagnostic test is its positive predictive value, a number that indicates how often a test, if positive, is right, Anderson says. In a disorder such as autism, which has a prevalence in the general population of about one in 88 births, even a few false positives very quickly render a test of limited value, he says. Based on his calculations using Van de Water's data and the prevalence of autism, "I get a positive predictive value of 16.5%, which is pretty bad." At that rate, only one out of six positive tests would actually be correct, he explains.

Goodman says that he came up with the same low positive predictive value after crunching the data provided in Van de Water's paper. "That assumes that you accept these numbers at face value, and I don't," he says. Based on the design of the study and his own analysis of the group's published data, he describes Pediatric Bioscience's claim that a positive result on a test for these antibodies will mean that a woman has a "99 percent" likelihood of having a child with autism as "completely false."

Van de Water and D'Alvise respond that the company's press release was "a bit unclear as written" and that likelihood "was not meant to convey likelihood in the statistical sense, but rather the 99% accuracy with which the study demonstrated specificity of the biomarkers for ASD." They also say that test is not meant to screen the general population but would be for women at higher risk of having autistic offspring, such as those who are older or who already have a child with developmental issues.

The U.S. Food and Drug Administration will not be required to review the accuracy or clinical validity of the Maternal Antibody Related Autism (MAR) test, as the company calls it, before it goes to market. Instead, D'Alvise says, Pediatric Bioscience will set up a blood testing lab under the Clinical Laboratory Improvement Amendments, a set of alternative federal standards that regulates diagnostic tests that only one laboratory has the expertise to run. "Typically this is the way new diagnostic tests get offered before they become mainstream," D'Alvise says.

Van de Water believes her test has predictive power, based on the relatively small population she's tested so far. But she acknowledges that it might not hold up in larger, more diverse populations. "I hope it is a valuable area to pursue—we think it is—but down the road who knows what will happen."

DiCicco-Bloom still isn't convinced that the maternal antibody test will bring much benefit and suggests that it could do more harm than good. "Pretty soon, everybody who worries about autism is going to be getting [tested], some for good reason, some because they're highly educated, motivated people," he says. "The moment that this test is given to physicians, it's not going to be controlled. No medical test ever is."

–EMILY UNDERWOOD

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IMMUNOLOGY

Bound for Glory

The discovery of antibodies that foil almost every HIV variant has transformed the AIDS vaccine search

In 2006, the International AIDS Vaccine Initiative (IAVI) launched a worldwide hunt to find the rarest of immune system warriors against HIV—antibodies that could thwart almost every known strain of the virus. IAVI, a New York City–based nonprofit, aptly gave the project a *Mission Impossible*–sounding moniker: Protocol G. If it succeeded, Protocol G promised to invigorate the failure-plagued HIV vaccine field and just possibly help design a product that could end the AIDS epidemic.

HIV at that point had thoroughly humbled vaccine researchers, time and again dodging any immune attack they could devise. More than 2 decades of effort had yet to bring a vaccine to market. But researchers had already glimpsed a weapon they hoped might turn the battle: so-called broadly neutralizing antibodies (bNAbs). Only a handful had been discovered, and even the best of them worked against only a few dozen of the hundreds of HIV strains that a vaccine would have to outwit to make a dent in the global epidemic.

The Protocol G team made an all-out effort to find more. Researchers analyzed 1800 blood samples taken from HIV-infected people in Zambia, South Africa, India, Thailand, Nigeria, Côte d'Ivoire, Rwanda, Uganda, Kenya, Australia, the United Kingdom, and the United States. After 2 years of combing through the sera, an effort led by IAVI team member Dennis Burton, an immunologist at the Scripps Research Institute in San Diego, California, homed in on one woman. By individually probing 30,000 of the woman's B cells, the immune actors that produce antibodies, they isolated two remarkable antibodies from her serum.

The two Protocol G antibodies jumped out because they "neutralized," or rendered incapable of establishing an infection, more than 70% of 162 divergent HIV strains, even at very low doses, Burton and co-workers explained in the 9 October 2009 issue of *Science*. Suddenly, creating a universal HIV vaccine seemed like more than just a wild dream. "It dawned on us that our little world was never going to be the same," Burton says.

Their little world had indeed turned upside down, and it had big world consequences. In short order, bNAbs became one of the hottest niches not just in HIV research but in immunology itself. Since 2009, researchers have identified more than 50 new HIV bNAbs, several of which look far better than those two from Protocol G.

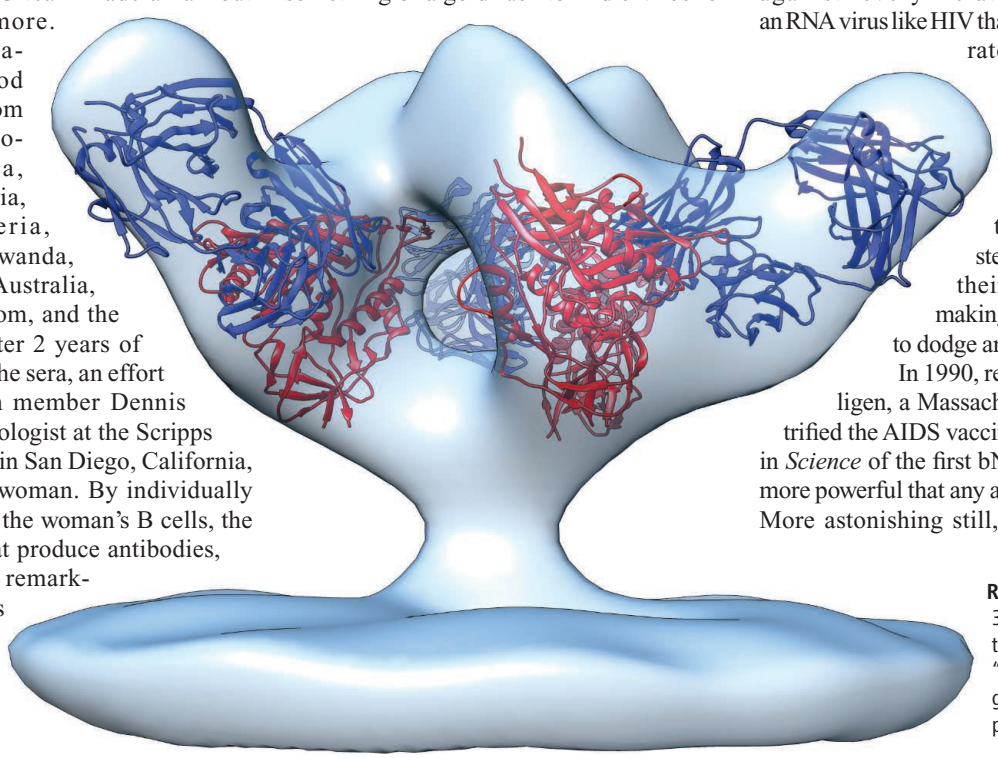
Dozens of labs are now trying to unravel the intricate pas de deux between HIV and the immune system that leads it to produce bNAbs, a process they hope to mimic one day with an immunogen—a harmless version of the virus used in a vaccine. And the activity in the HIV field has triggered something of a gold rush to find bNAbs for other diseases, including influenza (see sidebar, p. 1171), hepatitis C, dengue, and West Nile viruses. But researchers have no illusions about the challenge of coaxing the immune system to produce a type of antibody that it naturally generates only rarely and in tiny quantities. "If somebody came up with a real immunogen that would reproducibly elicit a broadly protective response, that would be fabulous," says David Baltimore, a Nobel Prize–winning virologist whose own group at the California Institute of Technology in Pasadena is attempting to genetically engineer stem cells to make bNAbs. "But I see a very difficult road."

Inauspicious start

Shortly after investigators proved in 1984 that HIV causes AIDS, the key obstacle to making a vaccine emerged. HIV reproduces at a breakneck speed, sloppily copying its genetic code each time. Many of the resultant mutants thrive, and the variants display different protein antigens. Antibodies, which normally target a single antigen with exquisite specificity, simply can't keep up with the ever-changing virus. As a result, neither the natural immune response nor the response induced by a conventional vaccine is effective.

Contrast this with viruses that vaccine-makers conquered. Measles virus has so little antigenic variation that an antibody response against one virus works against every relative. Even polio, an RNA virus like HIV that mutates at the same rate, can be derailed with a combination of antigens from three distinct strains of the virus. Unlike HIV, these viruses pay a steep fitness price when their antigens change, making it difficult for them to dodge antibody attacks.

In 1990, researchers from Repligen, a Massachusetts biotech, electrified the AIDS vaccine field with a report in *Science* of the first bNAb against HIV, far more powerful that any antibody seen to date. More astonishing still, they described the

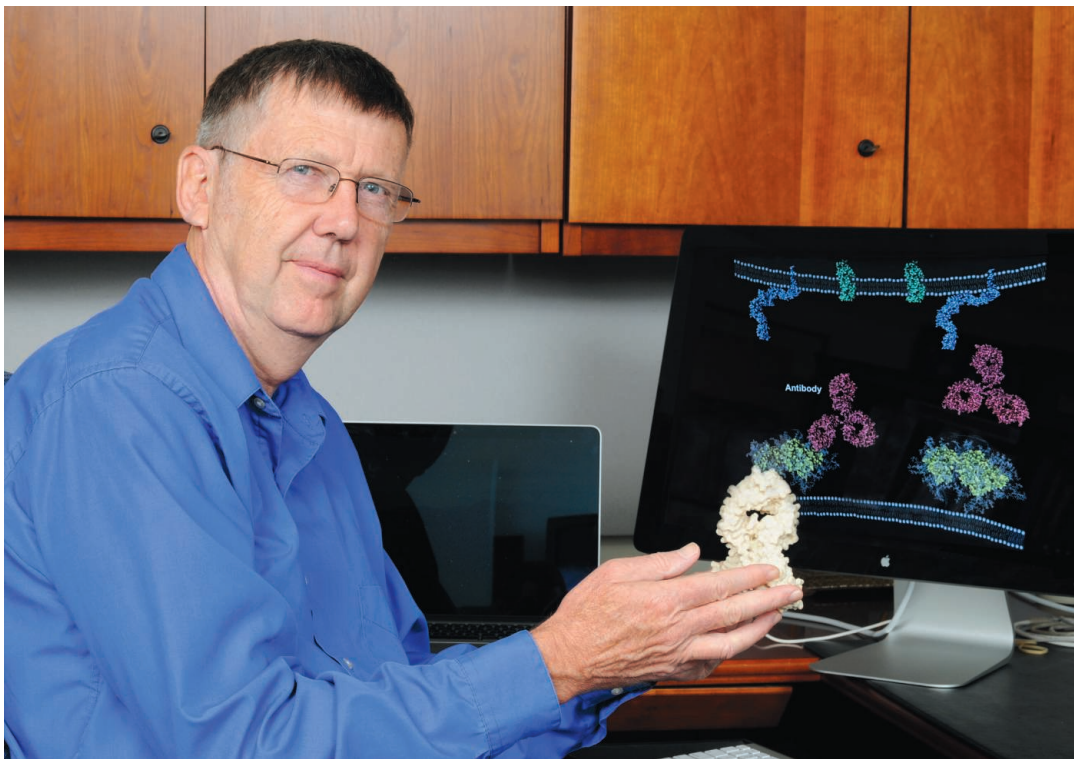


Resistance is futile. A 3D map from cryoelectron tomography of a "trimeric spike" of HIV's gp120 (red) bound by a potent bNAb (blue).

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Antibody hunter. Dennis Burton of Scripps holds a model of an HIV bNAb he bagged.

CREDITS (TOP TO BOTTOM): PHOTO BY DAVE FREEMAN, COURTESY OF THE SCRIPPS RESEARCH INSTITUTE; © ALFRED PASIEKA/SCIENCE SOURCE

exact viral component, or epitope, that stimulated the production of the antibody in animal experiments. A mere six amino acids at the tip of HIV's surface protein, gp120, taught the immune system how to stop diverse strains of the virus, they reported.

It sounded too good to be true. It was.

As it turned out, this bNAb was a laboratory artifact that worked only against strains of the virus grown in culture dishes, and it had no impact on "primary" isolates taken directly from infected people. That 1993 discovery (*Science*, 12 November, p. 980) scuttled hopes about the Repligen product. But the next year, Burton and colleagues at Scripps showed that by aspirating bone marrow from an HIV-infected man and then fishing out antibody genes, they had isolated a bNAb that worked against primary isolates.

To establish an infection, HIV first slips gp120 into a CD4 receptor on the surface of white blood cells. Some antibodies can bind to gp120 and neutralize it such that the virus can't enter the CD4 cell. But as HIV mutates, gp120 changes shape, evading antibodies. Burton's bNAb attached to a "conserved" part of gp120 that doesn't tolerate mutations because it is required by many variants to bind CD4 receptors. This bNAb crippled 17 of 24 primary isolates of the virus at what then seemed liked fantastically low doses (*Science*, 11 November 1994, p. 1024).

At roughly the same time in Austria, another group discovered bNAbs that worked on a different part of HIV. A team led by Hermann Katinger at the Institute of Applied Microbiology in Vienna identified two bNAbs that acted on gp41, a protein that spans the viral membrane and attaches to gp120, and were capable of neutralizing many HIV isolates. This finding suggested that the virus has more than one Achilles' heel.

Over the next decade, structural biologists like Ian Wilson at Scripps and Peter Kwong at the U.S. National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland, created high-resolution depictions of how these bNAbs bound to both gp120 and gp41. These exquisitely detailed images enabled the investigators to determine the precise mechanisms by which these antibodies tripped up the virus—and why other antibodies had such limited potency and breadth. But few other HIV bNAbs surfaced, and no one found antigens that could trigger their production in animal models or humans. At the same time, antibodies fell out of fashion with many vaccine researchers, who put more stock in stimulating killer cells, a kind of T lymphocyte. While antibodies prevent infection, killer cells identify and destroy cells that the virus manages to enter. Some groups contended that a T cell vaccine alone could stop the virus; others put their stock in a combination T cell/antibody vaccine. Still others rejected the notion of rationally designing a vaccine, pointing to a long history of vaccinologists who succeeded simply by testing various formulations in animals and people, paying little heed to immune mechanisms.



Also see the Antibodies special section, page 1191.

Working backward

Then, two developments reinvigorated the bNAb field.

First, high-profile, T cell–based vaccines against HIV failed miserably (*Science*, 10 September 2004, p. 1545 and 5 October 2007, p. 28), tilting more attention toward antibodies. On the second front, thanks to Protocol G and similar initiatives, the number of bNAbs available for study skyrocketed. Burton and others say that they owe their success to better lures to fish bNAbs from a sea of other antibodies. They also developed improved techniques to clone large numbers of antibodies from single B cells, first amplifying antibody genes and then putting them into viruslike vectors that spit out the products in bulk. For the first time, they could separate these faint immunologic signals from the noise. "Single cell antibody cloning changed the field," says immunologist Michel Nussenzweig, whose lab at Rockefeller University in New York City helped pioneer the technique for HIV bNAbs (see Review, p. 1199). "Otherwise you didn't even know what was in the human repertoires." An extraordinary level of multi-institution collaboration has given the endeavor a major boost, too, through IAVI's Neutralizing Antibody Consortium and two Centers for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID) created by NIAID.

With these advances, researchers can now find bNAbs, albeit at exceedingly low levels, in up to 25% of HIV-infected people. The bNAbs offer scant help to the already infected, as they come too late, when the virus has already infil-

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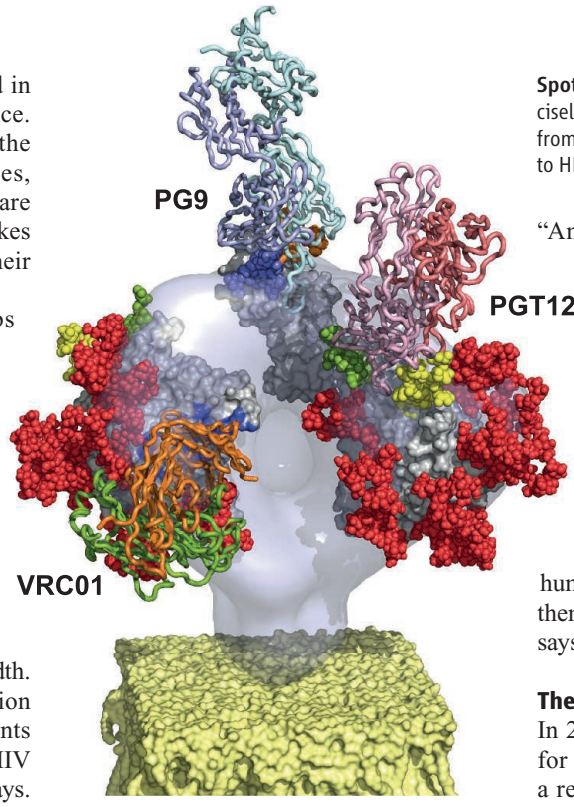
trated many blood cells and tissues, and in quantities too small to make a difference. But a vaccine that elicited bNAbs at the right moment, in sufficient quantities, might foil an infection. So researchers are now asking how the immune system makes these antibodies and what gives them their unusual powers.

Like other antibodies, HIV bNAbs emerge as the B cells first exposed to the virus multiply to produce clones that steadily develop more "affinity" for the invader. Called "affinity maturation," this process of mutation and selection ultimately favors the fittest immune response. But unlike other antibodies, bNAbs appear to evolve slowly over years, accumulating an unusually high number of mutations—three times as many as run-of-the-mill antibodies—which gives them their potency and breadth. The process appears to involve stimulation from different epitopes at different points in time. "There's an arms race between HIV and the immune system," Nussenzweig says. "As antibodies chase the virus around, it keeps changing, and the antibodies have to make more mutations."

Most mutations that give bNAbs their powers take place at the tips of the Y-shaped antibody molecules, which have loops that lasso viral epitopes. Among other things, bNAbs have evolved to become stickier than other antibodies, Nussenzweig and colleagues explained in the 30 September 2010 issue of *Nature*. That appears to be a response to one of HIV's unusual properties. The gp120 molecules studding HIV's surface form clusters of three called trimers. Each HIV has only about 10 trimers on its surface; on influenza viruses, in contrast, the surface proteins form about 450 trimeric spikes. "HIV is almost bald," Nussenzweig says. This dearth of trimers hampers antibodies: They bind most tightly to a virus when each arm of the Y can separately grab a different trimer. But the extra-sticky bNAbs can compensate by latching on to lipids that make up the HIV viral membrane or even to sugars that coat gp120.

Other peculiar features help HIV bNAbs stymie the virus. As Burton has shown, the loops at the tips of antibody arms are often extra long, increasing their ability to lasso an epitope. Nussenzweig discovered a second, related quirk. Antibody arms typically have a region that remains constant to provide a sturdy framework for the highly mutable loops. But Nussenzweig's group reported in the 28 March issue of *Cell* that HIV bNAbs shun convention, accumulating many mutations in the framework region that increase breadth and potency. For unknown reasons, these malleable framework regions don't compromise the stability an antibody needs to function. "It goes totally against the norm," Nussenzweig says. "Destabilizing something and making it better is counterintuitive."

Creating a vaccine that will elicit these features is a daunting assignment, say some researchers. "We're going to have to make this vaccine with nature's pathways and guidance," says Barton Haynes, an immunologist at Duke University in Durham, North Carolina, who heads a CHAVI-ID.



Spot on. Structural biologists have mapped precisely where two bNAbs from Protocol G and one from the Vaccine Research Center (ribbons) bind to HIV's gp120.

"And it's a vaccine the immune system doesn't favor making."

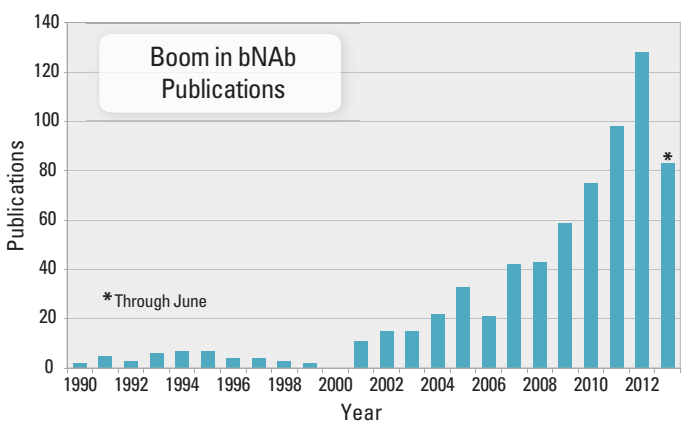
Nussenzweig is optimistic. "People don't invent vaccines *de novo*," he says. "In every case, you take a lesson from nature and try to copy it." Granted, people with HIV make potent bNAbs in only small amounts, but the discovery that dozens of different ones exist, each of which came about independently, provides hard proof that the human immune system knows how to make them. "If it can happen once," Nussenzweig says, "it can happen again."

The making of a bNAb

In 2006, a man in Malawi came to a clinic for sexually transmitted diseases that had a research project under way to try to find people within weeks of becoming infected with HIV. He met the criteria and joined the "acute infection" study, repeatedly donating blood, which enabled researchers to document changes over time in the gp120 of his virus, his antibody response, and ultimately the emergence of a bNAb. Now, this window into antibody evolution is inspiring a strategy to design a bNAb-based vaccine.

A large collaboration led by Duke's Haynes and John Mascola from NIAID's Vaccine Research Center studied the man's sequential blood samples. As the researchers explained in the 25 April issue of *Nature*, they traced the evolution of the antibody from the initial B cell response all the way to the bNAb, which emerged after more than a year. The original, or germline, antibody did not have much breadth, but it did bind avidly to the original "founder" virus that infected the man. A vaccine, they reason, should use gp120 from the founder virus to kickstart a B cell lineage that can ultimately produce a bNAb. Booster shots could then attempt to guide the mutation of the antibody genes in the cell to expand their breadth by using the same sequence of gp120 variants that naturally created the bNAb in the Malawian man.

In essence, the strategy amounts to carefully selecting a puppy from a litter and giving it the intensive training needed to



Paper trail. A PubMed search for "broadly neutralizing" shows a steep climb in reports.

CREDITS (TOP TO BOTTOM): D. CORTI AND A. LANZAVECCHIA, *ANNU. REV. IMMUNOL.* 31 (2013); PUBMED

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Published by AAAS

A Once-in-a-Lifetime Flu Shot?

No more yearly flu shots. An end to the threat of deadly pandemics. Far-fetched as those possibilities may sound, they could become reality if a hot new area of immunology pans out.

Flu vaccines trigger production of antibodies that attach to hemagglutinin, a protein on the surface of the virus that helps it infect cells. But hemagglutinin mutates so rapidly that antibodies to one human variant have limited power against another, requiring vaccinemakers to reformulate their shots each year. And when a novel animal flu jumps from birds or pigs into humans, existing immunity offers little defense and a pandemic can arise. Stopping it would require a new vaccine, which inevitably can't be developed quickly enough.

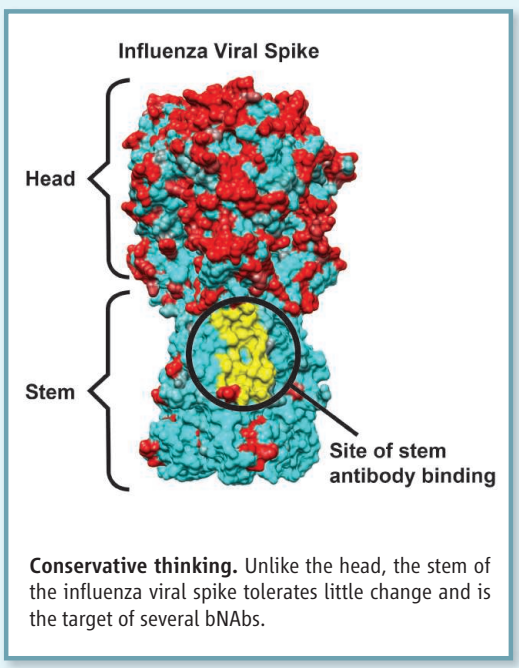
Recently, researchers have found a possible solution: "broadly neutralizing antibodies" (bNAbs) in humans to hemagglutinin, able to bind most, if not all, variants. Like bNAbs discovered for HIV (see main article, p. 1168), they have sparked provocative ideas about how to make a single vaccine that could thwart all strains of the virus.

In 2008, a Dutch biotech showed that such antibodies existed and that they worked by an unorthodox mechanism. In both test-tube and mouse experiments, the bNAb neutralized H5N1 and H1N1. (The "H" refers to hemagglutinin.) These highly divergent, dangerous influenza viruses caused, respectively, "bird flu" and the 1918 pandemic in humans. Unlike traditional antibodies to influenza, which bind to the highly mutable head of hemagglutinin, this one bound to more immutable amino acids in the highly conserved stem of the molecule.

Hopes ran high that a headless hemagglutinin could be the basis of a vaccine capable of triggering bNAbs that protected against all 17 different H subtypes. But creating a stem-only vaccine has presented formidable technical challenges. "Removing the head is extremely difficult if not impossible," says Antonio Lanzavecchia, an immunologist at the Institute for Research in Biomedicine in Bellinzona, Switzerland, whose team reported in the 12 August 2011 issue of *Science* the discovery of a stem-binding antibody that neutralized *every* H subtype. "You can't just cut it out." Basically, headless hemagglutinins fall apart.

Virologist Peter Palese's lab at the Icahn School of Medicine at Mount Sinai in New York City described a creative way around the problem in the June *Journal of Virology*. Even though people fail to make high levels of antibodies to the stem, they do make some and thus develop what's known as immunologic memory. So they reasoned that a vaccine might work if it had an engineered, chimeric hemagglutinin made from the stalk of a virus that humans had seen, triggering a robust memory response, with an "irrelevant" head that had circulated only in other species. They mimicked this chimeric vaccine in a mouse model, and it protected animals from distantly related flu viruses.

A research team at the National Institute of Allergy and Infectious Diseases has had impressive results in mice and ferrets with a different tack. The bNAbs to influenza are slow to develop in part because hemagglutinin naturally crowds the viral surface, hiding the stem regions of the protein from the immune system. Led by virologist Gary Nabel, the group described in the 4 July issue of *Nature* how it created an artificial, self-assembling nanoparticle called ferritin, an iron-storage protein, that expresses hemagglutinins at an unnatural angle, exposing their stalks. This new presentation of the protein leads to a potent bNAb response. Nabel, now chief scientific officer at vaccinemaker Sanofi, has high hopes that the days of seasonal flu shots are numbered. "We have the ability to steer the immune system back to where we want it to be," he says. **–J. C.**



Conservative thinking. Unlike the head, the stem of the influenza viral spike tolerates little change and is the target of several bNAbs.

CREDIT: G. J. NABEL AND A. S. FAUCI, *NATURE MEDICINE* 16, 12 (DECEMBER 2010) © 2010 NATURE AMERICA INC.

one day win the best of show. "It's ingenious that you'd prime with one epitope and boost with another epitope to chaperone the B cell response until the point that it's truly making a broadly neutralizing antibody," says immunologist Anthony Fauci, NIAID's director.

Burton, working with Scripps immunologist William Schief, also tracked the emergence of a bNAb, but they did so retrospectively. They started with a powerful bNAb and used genetic modeling to predict its ancestor's characteristics. Guided by what they learned, they hope to design a single immunogen that both tickles the right B cells into action *and* steers them to move from the germline antibody toward the mature bNAb. Unlike the Haynes group, Burton and Schief's team does not want to hold the immune system's hand and guide the germline B cell to make the bNAb. "Taking that too literally is likely to be asking for too much micromanagement," Schief says.

As the group explained in the 10 May issue of *Science*, a screen of massive gp120 libraries led to one that strongly bound both their putative germline antibody and the mature bNAb that evolved from it. The investigators then groomed this gp120 to contain little more than the epitope that both antibodies target. They now hope to show that they can elicit a bNAb response by "priming" the immune system with this artificial gp120, then following with a booster that contains trimer spikes in the most natural configuration possible.

Both the Burton/Schief team and Haynes's group have monkey studies under way to test their ideas. But even if they learn how to generate bNAbs, Fauci notes that a fundamental, proof-of-principle experiment has yet to happen: No one has shown that giving bNAbs to a person can prevent an infection. To that end, the Vaccine Research Center at NIAID hopes to soon launch human studies that passively give monoclonal bNAbs—which theoretically could last in the body a few months—to newborns of HIV-infected mothers and, separately, to adults at high risk of becoming infected. "Whether they're going to prevent acquisition of HIV is an open question," Fauci cautions.

Even if the bNAb strategy passes all these hurdles, years of testing will still be needed to prove that the vaccine protects people and is safe. But Fauci and many others at the forefront of the HIV vaccine search say bNAbs have brought a level of hope and common purpose that this fractious, battle-weary field has rarely, if ever, enjoyed.

–JON COHEN

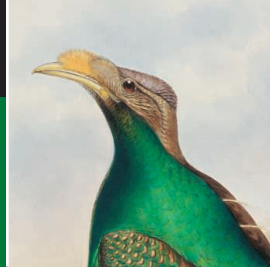
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DNA identification after conflict or disaster 1178

The science of biogeography 1182



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LETTERS

edited by Jennifer Sills

Turkey's Biodiversity Funding on the Rise

THE NEWS & ANALYSIS STORIES "FRAGILE WETLAND WILL TEST TURKEY'S RESOLVE IN PROTECTING biodiversity" and "For scientists, protests morph into fight for academic freedom" (J. Bohannon, 26 July, p. 332) deserve to be set in a wider context. Turkey is covered by three global biodiversity hot spots and has 3000 endemic plant species and nearly 100 endemic vertebrates (*1*). Its wetlands lie on one of the three principal migration routes for Eurasian birds wintering in Africa (*2*). One might therefore hope for a strong financial commitment to biodiversity conservation, not least because Turkey has ratified the Convention on Biological Diversity (*3*).

We compared Turkey's biodiversity funding to other countries' for 2001 to 2008. We used newly acquired data (*4*, *5*) to expand on a recent study (*6*) from which Turkey had been excluded due to inadequate information on its conservation financing. We estimate that Turkey's funding was $13.5 million U.S. dollars (USD) annually (mean for 2001 to 2008). This level of expenditure ranks Turkey as one of the 20 worst countries in the world for funding biodiversity, alongside countries such as Republic of the Congo and Côte d'Ivoire (*6*). Indeed, Turkey's own 2007 Biodiversity Action Plan states that "the insufficiency of [financial] resources…and the ineffective use of resources...draw attention" (*7*).



Aras River in Turkey.

Such substantial underfunding represents a potential extinction risk for both local and global biodiversity, including nearly 2000 threatened endemic plant species (*1*). However, there are recent, promising changes. Turkey's 2012 and 2013 conservation budget was triple the 2004 budget in real terms (*4*, *5*). This is roughly equivalent to jumping 20% up the rankings in 8 years (from 113th to 87th out of 128 countries analyzed). Turkey had also planted more trees than any other country except Ethiopia in 2009, even if largely in a production forestry context (*4*, *8*).

The new level of funding effort thus represents one large step forward, although many more steps are needed to halt biodiversity loss (*9*). For one, we strongly encourage Turkey's government to make the unusually high 2012 and 2013 budget commitments a new baseline for coming years, pending further improvement. We must also work to increase international donor contributions to biodiversity in Turkey, which fell from $6 million USD annually in 2000 to 2001 to $0.75 million USD in 2007 to 2008 (*10*). Regardless of funding, to improve its environmental performance, Turkey will have to enforce its environmental laws rather than dismantle them (*9*).

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Waiving Concerns About Conflicts of Interest

IN THEIR POLICY FORUM "UNCAPPING CONflict of interest?" (7 June, p. 1172), S. F. Wood and J. K. Mador argue for caps on the Food and Drug Adminstration (FDA) waivers of conflicts of interest (COIs) among members of advisory committees, but they do not identify substantial weaknesses in their arguments.

A systematic study by an FDA contractor tested and rejected the hypothesis that advisers with waived and disclosed COIs vote in favor of those interests more frequently than advisers with no such conflicts (*1*). Golec *et al*. independently report similar results (*2*). If advisers with disclosed COIs vote like advisers with no such conflicts on questions such as product approvals and blackbox warnings, it is not clear how limiting the number of committee members with COIs would improve committee recommendations.

Wood and Mador claim that many able and willing experts lack conflicts, but do not mention descriptions of unsuccessful searches for COI-free advisers typically found in the FDA's COI waivers [e.g., (*3*, *4*)]. Granting more COI waivers may increase

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the FDA's access to expertise, because advisers with waived COIs have more expertise than other advisers (*5*). The FDA, however, does not report (and may not collect) sufficient data to confirm whether the reduction in waivers has affected its access to expertise.

The authors critique FDA's focus on financial ties less than 12 months old, implying that grants and contracts that ended shortly before the 1-year window still constitute COIs. In fact, federal rules define a COI in terms of whether the particular matter—e.g., the drug approval—will have a direct and predictable effect on the adviser's financial interest (*6*), regardless of the time frame. Wood and Mador also fail to acknowledge the FDA's impartiality determinations (*7*, *8*), which cover noncurrent financial ties. Caps would have value if the system were otherwise flawed, but the FDA's processes are more robust than Wood and Mador acknowledge.

Finally, the authors do not address possible indirect effects of the COI waiver cap. The FDA's division directors, who identify most advisory committee experts, might prefer that each meeting avoid surpassing the COI waiver cap. If risk-averse, they might find such a strategy sensible because FDA leadership has stated that it would be better to have no COIs—even though forgoing expert advisers with COIs might leave the FDA with less access to expertise overall (*5*).

RANDALL LUTTER

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Response

THE IMPACT OF A FINANCIAL CONFLICT OF interest (COI) on individual decision making as part of a group is difficult to quantify, as noted by Lutter and discussed in our Policy Forum. However, because the U. S. Food and Drug Administration (FDA) is a science-based agency making critical decisions on approval and labeling of medical products, avoiding even an appearance of a COI is paramount. Indeed, public confidence depends on it. The FDA and its review divisions were quite successful in reducing the number of members of advisory committees with financial COIs, clearly demonstrating that the FDA is capable of identifying such individuals without increasing vacancy rates on the committees or reducing productivity.

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As Lutter identifies, there are indeed cases when specific experts are needed and it is necessary for the FDA to provide a waiver to allow them to serve. For example, certain pediatric specialties and some rare diseases may have few experts available who do not have a financial COI. The FDA, both in individual meetings and as a whole, was well below the previously required limits for waivers, so in these cases, waivers can and should be granted to conflicted experts.

But removing the legal limit on waivers—as was successfully done last year when there was no need to do so—raises real concerns. There was no problem to be fixed. Pressure seems to have been brought to bear on Congress and potentially on the FDA to increase the number of waivers beyond the limit, and to increase the number of advisory committee experts who have a financial interest in pharmaceutical or medical device product development.

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CORRECTIONS AND CLARIFICATIONS

Reviews: "Pivoting the plant immune system from dissection to deployment" by J. L. Dangl *et al*. (special section on Smarter Pest Control, 16 August, p. 746). In the Acknowledgments, two items were missing. Funding in the lab of J.L.D. on this topic is also supported by NSF grant IOS-0929410. B.J.S. is funded by NSF grants IOS-1146793 and BREAD-0965418 and NIH grant AI-087245. The HTML and PDF versions online have been corrected.

Reports: "Detection of a spinning object using light's orbital angular momentum" by M. P. J. Lavery *et al*. (2 August, p. 537). In the first full paragraph after equation 2, the phrase in parentheses should have appeared as "(small α, where $\sin \alpha \approx \alpha$)." The HTML and PDF versions online have been corrected.

TECHNICAL COMMENT ABSTRACTS

Comment on "Influence of HLA-C Expression Level on HIV Control"

Elisa Lo Monaco, Elisa Tremante, Priscilla Biswas, Martin P. Cranage, Donato Zipeto, Alberto Beretta, Patrizio Giacomini

Apps *et al*. (Reports, 5 April 2013, p. 87) found that high human leukocyte antigen C (HLA-C) expression favors HIV-1 control. However, as noted here, HLA-C was assessed with a monoclonal antibody (DT9) that cross-reacts with HLA-E. In the context of the available evidence, this is consistent with the idea that the two leukocyte antigens collaborate to keep the HIV-1 virus at bay.

Full text at http://dx.doi.org/10.1126/science.1241266

Response to Comment on "Influence of HLA-C Expression Level on HIV Control"

Richard Apps and Mary Carrington

Lo Monaco *et al*. propose that human leukocyte antigen E (HLA-E) and HLA-C expression levels both contribute to HIV control. The minimal, flat level of cell surface HLA-E detectable by staining with available HLA-E–specific antibodies questions a role for differential HLA-E expression in determining HIV control. Evidence remains far stronger that HLA-C expression levels as detected by the DT9 antibody specifically affect HIV control.

Full text at http://dx.doi.org/10.1126/science.1241854

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the past 3 months or matters of general interest. Letters are not acknowledged upon receipt. Whether published in full or in part, Letters are subject to editing for clarity and space. Letters submitted, published, or posted elsewhere, in print or online, will be disqualified. To submit a Letter, go to www.submit2science.org.

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Response to Comment on "Influence of HLA-C Expression Level on HIV Control"

Richard Apps[1,2] and Mary Carrington[1,2]*

Lo Monaco *et al*. propose that human leukocyte antigen E (HLA-E) and HLA-C expression levels both contribute to HIV control. The minimal, flat level of cell surface HLA-E detectable by staining with available HLA-E–specific antibodies questions a role for differential HLA-E expression in determining HIV control. Evidence remains far stronger that HLA-C expression levels as detected by the DT9 antibody specifically affect HIV control.

Lo Monaco *et al*. (*1*) suggest that our flow cytometry measurement of human leukocyte antigen C (HLA-C) expression could also detect HLA-E and propose an alternative interpretation of our data in which both of these antigens contribute to HIV control. However, published data indicate that HLA-E expression is poorly detected by flow cytometry of peripheral blood lymphocytes (PBLs) (*2*, *3*). Although an effect of HLA-E on HIV control is an interesting hypothesis, one would need to provide compelling data showing that the published findings regarding HLA-E expression levels are incorrect, that HLA-E is expressed at differential levels (which is not supported by any published staining data), and that HLA-E expression level affects HIV control.

The monoclonal antibody (mAb) DT9 was originally raised against tamarin major histocompatibility complex and subsequently found to bind all HLA-C alleles (with similar affinity), only very rare HLA-A or HLA-B alleles, and the nonclassical HLA-E molecule (*2*, *4*). We used flow cytometry with DT9 to measure HLA-C expression levels on PBLs from healthy donors (*2*, *5*), which was justified because HLA-C is expressed at substantially higher levels than HLA-E on PBLs. Indeed, the DT9 binding that we reported correlated both with donor HLA-C allotype and reverse transcription polymerase chain reaction (RT-PCR) measurement of HLA-C transcript levels, indicating that HLA-C is the antigen primarily detected by flow cytometry of PBLs with DT9 (*2*, *5*).

Lo Monaco *et al*. suggest that substantial levels of HLA-E can be detected on PBLs by cytometry based on a study from Corrah *et al*. that used the mAb 3D12, which recognizes HLA-E, but the staining with mAb 3D12 to PBLs in this study was negligible, averaging less than twofold above unstained controls (*3*). It was necessary for the authors to perform a statistical analysis from 30 donors to conclude that the 3D12 stain was any different from the control. This is in contrast to the robust cytometry staining of PBLs that we observe with several mAbs to HLA-C. It is not certain that even the very weak 3D12 binding to PBLs represents detection of HLA-E, because some cross-reactivity with classical HLA alleles has been reported for the mAb 3D12 (*6*). Indeed, Corrah *et al*. proceeded to use DT9 binding to reflect differences in HLA-C expression levels between individuals (*3*).

We had previously compared binding of the mAb MEM-E/08 (which binds only HLA-E) and the mAb DT9 (which binds HLA-E and HLA-C) to demonstrate that flow cytometry binding of DT9 to PBLs represents detection of HLA-C (*2*). The mAb MEM-E/08 bound at least as well as mAb DT9 to a transfectant expressing only HLA-E, demonstrating that MEM-E/08 is at least equivalent to DT9 in affinity for HLA-E. Alternatively, staining of PBLs was evident only with the mAb DT9 and not MEM-E/08, indicating that HLA-E levels on PBLs are below the threshold of detection and that DT9 reactivity with PBLs detects predominantly HLA-C. Lo Monaco *et al*. argue that mAb MEM-E/08 recognizes only β_2m-free antigen and that HLA-E is underestimated on PBLs, but the evidence that mAb MEM-E/08 recognizes β_2m-free HLA-E specifically is based on inconclusive isoelectric focusing analyses of HLA precipitations (*7*). More formal demonstration of the HLA-E conformations recognized by mAb MEM-E/08 along with an analysis of the HLA-E conformations present on PBLs, rather than cell lines, is needed to rule out the more parsimonious interpretation of our experiment, which is that binding of the mAb DT9 to PBLs detects predominantly HLA-C.

The argument that HLA-E expression substantially contributes to the pattern of DT9 binding is not supported by existing data. There are no measurements of HLA-E expression levels on PBLs showing that HLA-E varies between individuals in correlation with HLA-C allotype or the rs9264942 genotype, both of which mark DT9 binding in our studies. Rather, staining with the mAb 3D12 showed no correlation with rs9264942 genotype (*3*). HLA-A and -B are expressed at much higher levels than HLA-C on normal PBLs, so it is predominantly these antigens that will supply the leader peptide for HLA-E expression, adding further doubt to the possibility that HLA-E and -C levels correlate.

In contrast, the evidence for variation in HLA-C expression level that affects HIV control is substantial. HLA-C levels have now been shown to vary between individuals by multiple assays (microarray, RT-PCR, and flow cytometry). One of the mechanisms determining variation in HLA-C expression level involves a polymorphic microRNA binding site in the HLA-C 3′ untranslated region, which is absent in HLA-E (*8*). HLA-C expression levels marked by either rs9264942 genotype (*9*) or mAb DT9 staining (*5*) correlate with the frequency of HLA-C–restricted HIV-specific cytotoxic T lymphocyte responses and viral escape mutations in vivo.

Thus, there is no evidence that HLA-E expression levels approach those of HLA-C on PBLs or that HLA-E expression levels differ across individuals to give the patterns of DT9 binding that we detect. Therefore, we interpret our observations as demonstrating that differences in expression levels of HLA-C specifically across individuals correlate with control of HIV infection.

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Comment on "Influence of HLA-C Expression Level on HIV Control"

Elisa Lo Monaco,[1] Elisa Tremante,[1] Priscilla Biswas,[2] Martin P. Cranage,[3] Donato Zipeto,[4] Alberto Beretta,[2] Patrizio Giacomini[1]*

Apps *et al*. (Reports, 5 April 2013, p. 87) found that high human leukocyte antigen C (HLA-C) expression favors HIV-1 control. However, as noted here, HLA-C was assessed with a monoclonal antibody (DT9) that cross-reacts with HLA-E. In the context of the available evidence, this is consistent with the idea that the two leukocyte antigens collaborate to keep the HIV-1 virus at bay.

A report recently published in *Science* demonstrated that the control of HIV-1 infection is positively influenced by high human leukocyte antigen C (HLA-C) expression (*1*). We note that this observation largely relies on extensive flow cytometry testing with a monoclonal antibody (mAb) named DT9, and draw attention to the original paper in which this mAb was described to primarily bind HLA-E, HLA-C being secondarily detected as a result of cross-reactivity (*2*).

The claim by Apps *et al*. for operational HLA-C specificity of mAb DT9 is based on extensive background information previously presented by the same group, particularly the lack of coexpressed HLA-E on the surface of human peripheral blood mononuclear cells (PBMCs), as assessed by a mAb named MEM-E/08 (*3*). However, this finding has subsequently been challenged by Corrah *et al*., who have instead documented PBMC staining with another mAb to HLA-E, called 3D12 (*4*). Further adding to this controversy, and in agreement with Corrah *et al*., we have shown that mAb MEM-E/08 reacts with poorly expressed, unstable, unfolded HLA-E molecules free of their light chain subunit (β_2m). In addition, we found that HLA-E levels are often underestimated, because a fraction of HLA-E is surface-expressed as a tightly β_2m-associated conformer poorly reactive with the available mAbs, including to some extent even the conformational mAb 3D12 (*5*). Altogether, these results favor the possibility that HLA-E substantially contributes to DT9 reactivity on the surface of many different human cells. HLA-E cross-reactivity, even marginal, may not be negligible in this setting, since HLA-C is the lowest expressed classical class I molecule [reviewed in (*6*)].

On this basis, we suggest that mAb DT9 detects combined HLA-C/HLA-E expression and that this combination, rather than HLA-C alone, may be considered the most accurate readout for the outcome of HIV-1 infection. Essentially all the HLA-C alleles, but only some HLA-A and HLA-B alleles, encode signal sequences potentially acting as donors of stabilizing HLA-E ligands (*7*, *8*) (also see www.ebi.ac.uk/ipd/imgt/hla), providing direct insight into linked, and possibly coordinated, expression of HLA-C and HLA-E (Fig. 1). Coordination would result in HLA-E similarly contributing to DT9 binding in different HLA-C–expressing cells. Thus, HLA-E cross-reactivity would not preclude the discrimination of HLA-C–high from HLA-C–low alleles, a discrimination that is central to the HIV protection model put forward in several papers by the authors of (*1*). Protection from, and susceptibility to, HIV infection may then be interpreted in the context of a compound multilocus effect.

This alternative interpretation does not contradict, but rather complements, the original interpretation of Apps *et al*. (*1*). High HLA-C would incite cytotoxic T cell recognition, exactly as outlined by these authors, whereas high HLA-E may be instrumental in directing the lysis of virus-infected cells by certain HLA-E–restricted T cell subsets, as shown in the case of cytomegalovirus (*9*). Alternatively, or in addition, inhibitory HLA-E may engender a tolerogenic effect that paradoxically prevents the establishment of productive viral infection, as described in a macaque model of simian immunodeficiency virus vaccination (*10*).

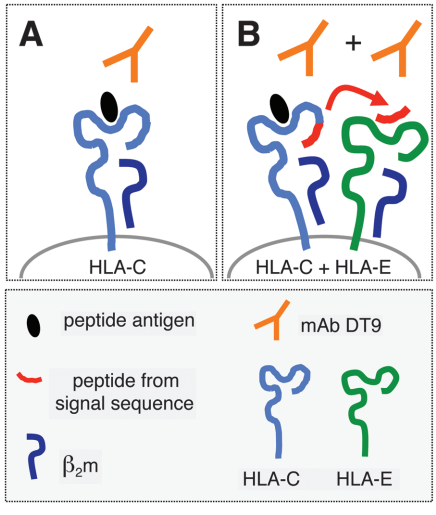


Fig. 1. HLA-C and HLA-E: linked expression, reactivity with mAb DT9, and possible collaborative protection from HIV-1. Two patterns of mAb DT9 reactivity are depicted, implying different HIV-1 control models. The first (**A**), proposed by Apps *et al*., is based on a restricted HLA-C reactivity of DT9 and is consistent with demonstrated, HLA-C–specific protective effects (*1*, *11*). The second (**B**), hypothesized here on the basis of the previously observed HLA-E cross-reactivity with DT9, envisages a compound multilocus effect. Because HLA-E requires peptides donated from the signal sequence of HLA-C for its stable assembly with β_2m, we suggest that the two class I HLA molecules are coordinately expressed: The higher HLA-C is, the higher is the surface HLA-E pool. Because they are expressed in proportional amounts, HLA-E does not prevent the appreciation of differences in HLA-C expression by mAb DT9. Evidence for a protective role of HLA-E remains so far indirect.

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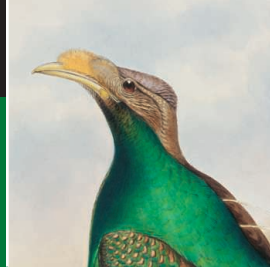
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DNA identification after conflict or disaster 1178

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LETTERS

edited by Jennifer Sills

Turkey's Biodiversity Funding on the Rise

THE NEWS & ANALYSIS STORIES "FRAGILE WETLAND WILL TEST TURKEY'S RESOLVE IN PROTECTING biodiversity" and "For scientists, protests morph into fight for academic freedom" (J. Bohannon, 26 July, p. 332) deserve to be set in a wider context. Turkey is covered by three global biodiversity hot spots and has 3000 endemic plant species and nearly 100 endemic vertebrates (*1*). Its wetlands lie on one of the three principal migration routes for Eurasian birds wintering in Africa (*2*). One might therefore hope for a strong financial commitment to biodiversity conservation, not least because Turkey has ratified the Convention on Biological Diversity (*3*).

We compared Turkey's biodiversity funding to other countries' for 2001 to 2008. We used newly acquired data (*4*, *5*) to expand on a recent study (*6*) from which Turkey had been excluded due to inadequate information on its conservation financing. We estimate that Turkey's funding was $13.5 million U.S. dollars (USD) annually (mean for 2001 to 2008). This level of expenditure ranks Turkey as one of the 20 worst countries in the world for funding biodiversity, alongside countries such as Republic of the Congo and Côte d'Ivoire (*6*). Indeed, Turkey's own 2007 Biodiversity Action Plan states that "the insufficiency of [financial] resources…and the ineffective use of resources...draw attention" (*7*).



Aras River in Turkey.

Such substantial underfunding represents a potential extinction risk for both local and global biodiversity, including nearly 2000 threatened endemic plant species (*1*). However, there are recent, promising changes. Turkey's 2012 and 2013 conservation budget was triple the 2004 budget in real terms (*4*, *5*). This is roughly equivalent to jumping 20% up the rankings in 8 years (from 113th to 87th out of 128 countries analyzed). Turkey had also planted more trees than any other country except Ethiopia in 2009, even if largely in a production forestry context (*4*, *8*).

The new level of funding effort thus represents one large step forward, although many more steps are needed to halt biodiversity loss (*9*). For one, we strongly encourage Turkey's government to make the unusually high 2012 and 2013 budget commitments a new baseline for coming years, pending further improvement. We must also work to increase international donor contributions to biodiversity in Turkey, which fell from $6 million USD annually in 2000 to 2001 to $0.75 million USD in 2007 to 2008 (*10*). Regardless of funding, to improve its environmental performance, Turkey will have to enforce its environmental laws rather than dismantle them (*9*).

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Waiving Concerns About Conflicts of Interest

IN THEIR POLICY FORUM "UNCAPPING CONflict of interest?" (7 June, p. 1172), S. F. Wood and J. K. Mador argue for caps on the Food and Drug Adminstration (FDA) waivers of conflicts of interest (COIs) among members of advisory committees, but they do not identify substantial weaknesses in their arguments.

A systematic study by an FDA contractor tested and rejected the hypothesis that advisers with waived and disclosed COIs vote in favor of those interests more frequently than advisers with no such conflicts (*1*). Golec *et al*. independently report similar results (*2*). If advisers with disclosed COIs vote like advisers with no such conflicts on questions such as product approvals and blackbox warnings, it is not clear how limiting the number of committee members with COIs would improve committee recommendations.

Wood and Mador claim that many able and willing experts lack conflicts, but do not mention descriptions of unsuccessful searches for COI-free advisers typically found in the FDA's COI waivers [e.g., (*3*, *4*)]. Granting more COI waivers may increase

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the FDA's access to expertise, because advisers with waived COIs have more expertise than other advisers (*5*). The FDA, however, does not report (and may not collect) sufficient data to confirm whether the reduction in waivers has affected its access to expertise.

The authors critique FDA's focus on financial ties less than 12 months old, implying that grants and contracts that ended shortly before the 1-year window still constitute COIs. In fact, federal rules define a COI in terms of whether the particular matter—e.g., the drug approval—will have a direct and predictable effect on the adviser's financial interest (*6*), regardless of the time frame. Wood and Mador also fail to acknowledge the FDA's impartiality determinations (*7*, *8*), which cover noncurrent financial ties. Caps would have value if the system were otherwise flawed, but the FDA's processes are more robust than Wood and Mador acknowledge.

Finally, the authors do not address possible indirect effects of the COI waiver cap. The FDA's division directors, who identify most advisory committee experts, might prefer that each meeting avoid surpassing the COI waiver cap. If risk-averse, they might find such a strategy sensible because FDA leadership has stated that it would be better to have no COIs—even though forgoing expert advisers with COIs might leave the FDA with less access to expertise overall (*5*).

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Response

THE IMPACT OF A FINANCIAL CONFLICT OF interest (COI) on individual decision making as part of a group is difficult to quantify, as noted by Lutter and discussed in our Policy Forum. However, because the U. S. Food and Drug Administration (FDA) is a science-based agency making critical decisions on approval and labeling of medical products, avoiding even an appearance of a COI is paramount. Indeed, public confidence depends on it. The FDA and its review divisions were quite successful in reducing the number of members of advisory committees with financial COIs, clearly demonstrating that the FDA is capable of identifying such individuals without increasing vacancy rates on the committees or reducing productivity.

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As Lutter identifies, there are indeed cases when specific experts are needed and it is necessary for the FDA to provide a waiver to allow them to serve. For example, certain pediatric specialties and some rare diseases may have few experts available who do not have a financial COI. The FDA, both in individual meetings and as a whole, was well below the previously required limits for waivers, so in these cases, waivers can and should be granted to conflicted experts.

But removing the legal limit on waivers—as was successfully done last year when there was no need to do so—raises real concerns. There was no problem to be fixed. Pressure seems to have been brought to bear on Congress and potentially on the FDA to increase the number of waivers beyond the limit, and to increase the number of advisory committee experts who have a financial interest in pharmaceutical or medical device product development.

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CORRECTIONS AND CLARIFICATIONS

Reviews: "Pivoting the plant immune system from dissection to deployment" by J. L. Dangl *et al*. (special section on Smarter Pest Control, 16 August, p. 746). In the Acknowledgments, two items were missing. Funding in the lab of J.L.D. on this topic is also supported by NSF grant IOS-0929410. B.J.S. is funded by NSF grants IOS-1146793 and BREAD-0965418 and NIH grant AI-087245. The HTML and PDF versions online have been corrected.

Reports: "Detection of a spinning object using light's orbital angular momentum" by M. P. J. Lavery *et al*. (2 August, p. 537). In the first full paragraph after equation 2, the phrase in parentheses should have appeared as "(small α, where $\sin \alpha \approx \alpha$)." The HTML and PDF versions online have been corrected.

TECHNICAL COMMENT ABSTRACTS

Comment on "Influence of HLA-C Expression Level on HIV Control"

Elisa Lo Monaco, Elisa Tremante, Priscilla Biswas, Martin P. Cranage, Donato Zipeto, Alberto Beretta, Patrizio Giacomini

Apps *et al*. (Reports, 5 April 2013, p. 87) found that high human leukocyte antigen C (HLA-C) expression favors HIV-1 control. However, as noted here, HLA-C was assessed with a monoclonal antibody (DT9) that cross-reacts with HLA-E. In the context of the available evidence, this is consistent with the idea that the two leukocyte antigens collaborate to keep the HIV-1 virus at bay.

Full text at http://dx.doi.org/10.1126/science.1241266

Response to Comment on "Influence of HLA-C Expression Level on HIV Control"

Richard Apps and Mary Carrington

Lo Monaco *et al*. propose that human leukocyte antigen E (HLA-E) and HLA-C expression levels both contribute to HIV control. The minimal, flat level of cell surface HLA-E detectable by staining with available HLA-E–specific antibodies questions a role for differential HLA-E expression in determining HIV control. Evidence remains far stronger that HLA-C expression levels as detected by the DT9 antibody specifically affect HIV control.

Full text at http://dx.doi.org/10.1126/science.1241854

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the past 3 months or matters of general interest. Letters are not acknowledged upon receipt. Whether published in full or in part, Letters are subject to editing for clarity and space. Letters submitted, published, or posted elsewhere, in print or online, will be disqualified. To submit a Letter, go to www.submit2science.org.

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ECONOMICS AND HEALTH

A Flawed Diagnosis

José A. Tapia Granados

The Body Economic
Why Austerity Kills: Recessions, Budget Battles, and the Politics of Life and Death

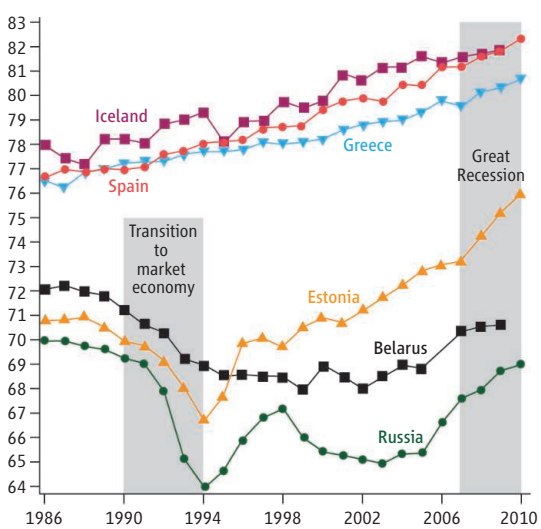
by David Stuckler and Sanjay Basu
Basic Books, New York, 2013. 238 pp. $25.99. ISBN 9780465063987.
Allen Lane, London, £20. ISBN 9781846147838.

In a journalistic style, the engaging and ambitious *The Body Economic* jumps from economic to political to health issues, intermingling academic discussions with plenty of human-interest anecdotes. Overall, David Stuckler and Sanjay Basu present a picture in which Keynesian economics is the magic wand that fixes the economy and promotes health. Iceland, the New Deal, Sweden, and Britain under Labour are models for health and economic policy, while Greece, Spain, and Britain under the Conservative David Cameron are bad experiences to be avoided. By defending public spending, the "good guys"—Franklin D. Roosevelt, Barack Obama, Aneurin Bevan, Joseph Stiglitz, Paul Krugman—promote a vibrant economy and a healthy population, whereas the "bad guys"—Milton Friedman, Jeffrey Sachs, Angela Merkel, bankers, and the International Monetary Fund—bring on economic decay and disease. Unfortunately, things are a little bit more complex.

The book is divided into three parts: "History," "The Great Recession," and "Resilience." Nonetheless, it offers little discussion of the history behind the current state of economics—a discipline divided into many schools that strongly disagree on fundamental issues. Reading *The Body Economic* might leave one with the impression that Keynesian economic remedies are as clear and straightforward as choosing to drink water when one is thirsty. Actually, there is strong disagreement (for a variety of reasons) on whether Keynesian policies work and about specific policies (such as the appropriate size of the national debt) even among Keynesians themselves. Stuckler (a sociologist at Oxford University) and Basu (an epidemiologist at Stanford University) largely ignore these debates and assert repeatedly that public spending is the solution to economic and health ailments. In their view, the evidence showing that that is the case would be disputed only by those oblivious to the interests of the population.

The Body Economic has little to say on previous investigations of the impact of macroeconomic factors on health. Early in the 20th century, Dorothy Thomas and William Ogburn were surprised to find that, in Britain, death rates rose during periods of prosperity and decreased during recessions (*1*). This pattern, which has been repeatedly documented in market economies around the world, is paradoxical because at the individual level unemployment or lower income are associated with lower levels of health and higher risk of death. As recessions in market economies are times of higher unemployment and lower incomes, one would expect mortality increases, but instead one observes mortality decreases. Regrettably, Stuckler and Basu discard without much consideration the overwhelming evidence supporting this "healthy recession paradox."

Because disease in populations is hard to quantify, population health is often measured by death rates summarized in the form of life expectancy at birth (LEB), a measure that accounts for differences in age structures across populations over time. LEB figures show that health strongly deteriorated in the early 1990s in Russia during the transition to a market economy, a fact that the authors discuss at length in the chapter "The Post-Communist Mortality Crisis." But LEB data also show that population health actually improved in Greece (and nearly all countries in Europe) between 2007 and 2010, during the Great Recession (see figure). This counterintuitive outcome goes unmentioned in *The Body Economic*. Instead, we read that in recent years, "Greece's health has begun to resemble that of Russia in the aftermath of Shock Therapy and mass privatization"—a surprising assertion that is quite at odds with the facts.



At odds with the authors' claims. Life expectancy at birth (LEB) for six European countries, 1986 to 2010 (*2*).

One of the principal claims in *The Body Economic* is that austerity is bringing disaster to countries such as Greece or Spain where it has been applied, while in Iceland, where austerity was not applied, "public health actually improved during the recession." Stuckler and Basu justify their position by citing increases in cases of AIDS, infectious encephalitis, and suicides. Unfortunately, this selective presentation of statistics does not give the whole picture. In fact, LEB in Greece rose from 79.6 years in 2007 to 80.3 years in 2009, while over the same period LEB in Iceland increased from 81.6 to 81.9 years. Therefore, during the two years following the start of the Great Recession, population health actually improved in both Greece and Iceland, but the improvement in Greece (0.7 year) was more than twice that observed in Iceland (0.3 year).

Measures such as LEB or the age-adjusted death rate for all causes of death indicate that population health improves during recessions. Suicide rates do not conform to this pattern, as they generally increase during recessions and decline during expansions. Stuckler and Basu claim that before the Great Recession, "Greece had the lowest suicide rate in Europe," but now (as part of a public health disaster) "that rate has doubled." This seems to suggest an explosive increase of suicides in the country. Available World Health Organization figures, however, suggest only a moderate increase of suicides in Greece between 2007 and 2010. The increase is much smaller than in, say, Norway or the Netherlands, and the suicide rate in Greece remains by far very low compared with the rates in other European countries.

High levels of unemployment and falling incomes are causing serious distress in many parts of the world. In Europe, austerity policies are cutting social services, privatizing health care, and reducing public investment when these are most needed to provide income and social welfare. Although recessions and austerity policies may have many adverse social con-

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sequences, their effects on health are likely much more nuanced and complex than Stuckler and Basu suggest. For instance, evidence indicates that periods of high growth in market economies raise the risks of heart attacks, industrial and traffic injuries, and respiratory disease. Conversely, these particular risks decrease in recessions.

The case that Stuckler and Basu present for their conclusion that austerity kills is undermined by exaggerated claims. Overall, *The Body Economic* does not shed much light on many of the processes by which our health is influenced in complex and counterintuitive ways by the economic system in which we live and work. Nonetheless, the timely book covers interesting material and tells a story many want to hear.

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EXHIBITION: ANTHROPOLOGY

Portraits from a Collision

Caroline Ash

Perhaps it was the capture of his mother as a girl and the stories he subsequently heard as a child that motivated George Catlin (1796–1872) to appoint himself the cultural historian of American Indians. Whatever the reasons, in the 1830s this self-taught artist traveled on five expeditions to western North America, painted 500 portraits, made copious notes and collections, and wrote several books (some of which are still in print). All together, these constitute an elegy, as he saw it, to the imminent extinction of indigenous peoples in collision with white expansionism. That some of Catlin's artistry should return to Europe, courtesy of the Smithsonian Trust, UK, is fitting, for Catlin's collection was shown in London during the 1840s in the Egyptian Hall at Piccadilly, just a few streets away from the National Portrait Gallery, where his portraits were hung this spring. Although the London exhibition has now closed, a sample of the more than 50 portraits it included (along with commentary on Catlin's work and life) can be viewed at the National Portrait Gallery's website. In addition, the Smithsonian American Art Museum maintains a virtual exhibition on Catlin and his "Indian Gallery" of the late 1830s (*1*).

Catlin thought of himself as a contributor to the "science of man"; hence the portraits are of a type, quite formal, often in the same posture, and painted with a limited palette. Nonetheless, some among them are great depictions of independence, pride, and disdain. The artist seems to have known some of his subjects well. The portraits are affecting, not just because we know that the fate of some of the sitters was uncertain and grim and that whole peoples were concurrently suffering genocide, but also because across some of the faces we discern flickers of opinions, thought, and words almost spoken.



Field work. Catlin's *La-dóo-ke-a, Buffalo Bull, a Grand Pawnee Warrior* (1832) lacks the finished body and costume details that the artist usually completed in his studio.

CREDIT: SMITHSONIAN AMERICAN ART MUSEUM/ART RESOURCE, NY

George Catlin
American Indian Portraits

Stephanie Pratt and Joan Carpenter Troccoli, curators
National Portrait Gallery, London, in association with the Smithsonian American Art Museum. Through 23 June 2013. www.npg.org.uk/whatson/george-catlin-american-indian-portraits/exhibition.php

George Catlin
American Indian Portraits

by Stephanie Pratt and Joan Carpenter Troccoli
National Portrait Gallery, London. 2013. 190 pp. £25. ISBN 9781855144576

Catlin's motives were undoubtedly complex, and in his time, traveling shows with dancing American Indians, although now considered prurient, were an acceptable way of earning a living. Tragically, Catlin was not cut out to be a showman. His world unraveled while on tour in Brussels and Paris, when several of his Objiwa colleagues died of smallpox and his wife and son perished from pneumonia and meningitis. Failing in attempts to sell his collection to the U.S. government, Catlin went bankrupt in London in 1852. To help meet his debts, the portraits and related artifacts were purchased by the American industrialist Joseph Harrison, Jr. (whose widow ultimately bequeathed them to the Smithsonian Institution). After various adventures during nearly two, poorly documented decades spent hiding from creditors, Catlin worked in a studio at the Smithsonian during the last months of his life.

Despite the showmanship, Catlin did not peddle the easy stereotype of the buckskin-clad warrior haloed by feathers; he took trouble to explain how varied and complex Native American culture was. Catlin evidently respected the people he portrayed. Perhaps his legacy offers some consolation for his often tormented and embittered life: His portraits are considered sufficiently authentic to be consulted by scholars and Indians wanting to rebuild cultural heritage.

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PUBLIC HEALTH

DNA Identification After Conflict or Disaster

International structures are needed to promote more equitable access to forensic identification and ensure uniform protections for participants.

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Over the last 30 years, DNA profiling has been used to identify human remains that are so badly damaged, comingled, or decayed that they might otherwise have been lost to history (*1*). Despite growing recognition of the importance of forensic identification to promote the welfare and rights of survivors of large-scale conflict or natural disaster, access to it is often piecemeal and ad hoc.

Large-scale national and international efforts to identify victims of repression and mass violence have been undertaken in the Western Balkans (*2*), Argentina (*3*), and elsewhere in the Americas (*4*). Other victims of mass death around the world, particularly those in Africa and Asia, have received much less attention (*5*). After the 2004 tsunami, international efforts to identify the remains of victims were undertaken in Thailand, where there was a high density of Western tourists, but not in Sri Lanka, Indonesia, or other affected areas (*6*). After the 2010 earthquake in Haiti, foreign investigators had a mandate to recover their own citizens but not to provide significant assistance to the recovery of Haitians (*7*).



Families of the missing struggle to obtain information and compensation. Bangladeshi relatives hold photos of the missing and dead workers 3 days after a building collapsed on 27 April 2013. Lack of resources for DNA identification has delayed identification of the missing.

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In the context of poverty and deprivation, forensic identification might appear to be a luxury. But access to scientific identification of the missing and the dead after mass casualty events can be a starting point for healing, reconstruction, and the ability to access financial resources or to regain or maintain social status. Perpetrators of political violence and oppression seek to erase people, deny crimes, and rewrite history. Where there has been the social will to use it, DNA identification technology has provided a powerful tool to establish the identities of the disappeared and anchor truth against denial (*2*, *8*). For example, after the 1995 massacre of more than 8000 Muslim men and boys at Srebrenica in Bosnia and Herzegovina, Bosnian Serbs sought to hide the evidence of their crimes. Bodies were stripped of identity markers, such as wallets and personal possessions, before they were buried in mass graves. Then, they were dug up, moved, and reburied when the original graves were about to be discovered by the international community. The use of DNA by the International Commission on Missing Persons (ICMP) was often the only way to establish the identity of the missing under such circumstances (*2*).

The large-scale DNA identification effort undertaken by ICMP was not initially proposed by the international community or even local political groups. It emerged out of persistent demands by families of the missing for justice for themselves and their loved ones and for perpetrators to be held accountable (*2*, *9*, *10*). Similar demands for justice have been made by family members across Latin and South America, Asia, Africa, and the Middle East.

Access to identification technology can determine whether relatives of the missing are able to exercise a range of civil and social rights necessary to secure their welfare (*9*, *10*). In Nepal, after a decade of conflict between the government and Maoist rebels, many elderly parents and poor women have been left indigent by the disappearance of working children or spouses (*9*). Without identification of a missing breadwinner, families deprived of income may be unable to access financial resources, seek restitution, or dispose of personal property. In Bosnia and Herzegovina, wives of the missing could not access pensions without confirmation of their husbands' death. Rumors that their husbands were alive in prison camps prevented many from accepting certifications of death that were not based on forensic evidence (*10*). Without recogni-

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tion of their status as bereaved and the ability to remarry, psychologically traumatized spouses and families become socially stigmatized and marginalized (*11*). Wives of the missing in rural Nepal are often unable to remarry or live independently because they are culturally bound to behave as married women in dress, demeanor, and activity. Those fortunate enough to be supported by the families of their missing husbands face resentment at home and increasing isolation in their communities (*9*).

For multiple reasons, formalized international structures are needed to promote more equitable access to scientific identification techniques, ensure their fair and efficient use, and provide uniform protections to participants after large-scale conflict and disaster.

First, resource limitations in many countries make it difficult to establish sufficient capacity to perform large-scale scientific identifications or to purchase the relevant materials and services from commercial vendors. Formalized international structures would address humanitarian and human rights goals by promoting access to forensic identification on terms other than ability to pay.

Second, large-scale identification efforts are complex undertakings that require coordination of many different groups and the harmonization of practices and policies. The efficiency of such activities could be increased by utilizing structures with standing operational and logistical capacity to quickly and efficiently implement standardized procedures. For example, confusion over procedures for identifying and returning the remains of victims of the April 2013 collapse of the Rana Plaza factory building in Bangladesh resulted in bodies being returned to the wrong families. The need to use DNA to identify badly damaged remains overwhelmed local laboratory capacity, and delays fed accusations that the government was trying to avoid having to pay compensation to families. (*12*).

Third, expanding access to forensic identification technologies will not advance humanitarian and social goals unless participants can be confident that those carrying out the identification process have the mandate and the authority to protect their rights and welfare (*13*). Variation in local norms, political climate, and legal protections make it difficult to ensure uniform protections for the human rights and welfare of participants in identification efforts. Moreover, identification efforts frequently cross national boundaries or involve multiple jurisdictions and are carried out by diverse groups. Thus, international structures are needed to prevent material and information gathered for identification purposes from being used for any purpose not directly related to the identification of the missing (*13*).

DNA identification through kinship matching requires the willingness of multiple relatives to contribute DNA samples so that databases can be created to facilitate profile matching. Coupled with the familial nature of DNA, this process can expose participants to risks that are unnecessary, disproportionate, or unfair if government authorities or private actors attempt to use samples or information gathered for identification purposes for other ends (*14*). For example, such databases can reveal discrepancies between reported kinship relationships and biological relatedness. In places where infidelity is treated as a crime, where women are held responsible for pregnancies that result from rape, or where women's rights are not robustly protected in law or by its enforcement, there may be strong incentives to use such findings to uphold norms of fidelity and propriety. Similar incentives may tempt authorities to use DNA profiles to identify family members who may be exposed to differential scrutiny in conducting criminal investigations or attempting to identify political activists.

Furthermore, current scientific limitations on the information that can be gleaned from DNA databases created for identification purposes are unlikely to persist (*15*). Given the speed of advancing DNA technology (*15*), there is a need to be proactive in establishing strong norms limiting the uses that can be made of such databases. Formalized international structures should provide explicit legal assurance that biological samples and DNA databases are secure and cannot be accessed by state or nonstate actors for purposes other than identification of the missing.

Fourth, to ensure that forensic identification advances human rights goals, international structures must have explicit mechanisms to facilitate the use of identification information as evidence in legal proceedings against those who are responsible for the death or disappearance of the missing. However, there must be explicit legal assurance that such efforts directly advance the interests of participants in identification efforts, that the privacy of participants will be strictly protected, and that their information will only be used if they give explicit informed consent.

The validity and integrity of forensic identifications are essential to promoting social trust in their results and to the admissibility of forensic evidence in legal proceedings. Formalized international structures therefore should contain explicit mechanisms for quality assurance, audit, and review, as well as to ensure that the privacy of donors is not compromised. Through economies of scale and the use of standing expertise, such structures should promote rigorous scientific practices across identification efforts at lower cost than might be achieved by ad hoc initiatives.

Formalized international structures could take many forms, from a single international institution to a decentralized network of agencies. More important than their specific form, however, is their clear commitment to promoting more equitable access to forensic identification; fair and efficient use of this technology; strong, legally binding protections for participants; and the ability to use forensic evidence to advance the cause of justice and human rights.

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A Once-in-a-Lifetime Flu Shot?

No more yearly flu shots. An end to the threat of deadly pandemics. Far-fetched as those possibilities may sound, they could become reality if a hot new area of immunology pans out.

Flu vaccines trigger production of antibodies that attach to hemagglutinin, a protein on the surface of the virus that helps it infect cells. But hemagglutinin mutates so rapidly that antibodies to one human variant have limited power against another, requiring vaccinemakers to reformulate their shots each year. And when a novel animal flu jumps from birds or pigs into humans, existing immunity offers little defense and a pandemic can arise. Stopping it would require a new vaccine, which inevitably can't be developed quickly enough.

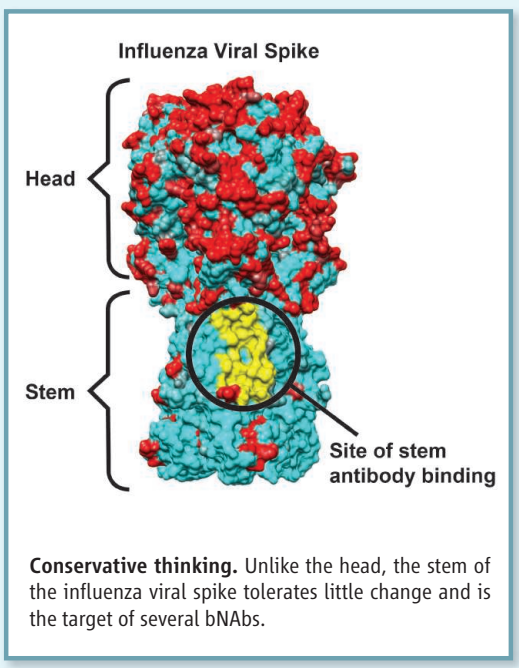
Recently, researchers have found a possible solution: "broadly neutralizing antibodies" (bNAbs) in humans to hemagglutinin, able to bind most, if not all, variants. Like bNAbs discovered for HIV (see main article, p. 1168), they have sparked provocative ideas about how to make a single vaccine that could thwart all strains of the virus.

In 2008, a Dutch biotech showed that such antibodies existed and that they worked by an unorthodox mechanism. In both test-tube and mouse experiments, the bNAb neutralized H5N1 and H1N1. (The "H" refers to hemagglutinin.) These highly divergent, dangerous influenza viruses caused, respectively, "bird flu" and the 1918 pandemic in humans. Unlike traditional antibodies to influenza, which bind to the highly mutable head of hemagglutinin, this one bound to more immutable amino acids in the highly conserved stem of the molecule.

Hopes ran high that a headless hemagglutinin could be the basis of a vaccine capable of triggering bNAbs that protected against all 17 different H subtypes. But creating a stem-only vaccine has presented formidable technical challenges. "Removing the head is extremely difficult if not impossible," says Antonio Lanzavecchia, an immunologist at the Institute for Research in Biomedicine in Bellinzona, Switzerland, whose team reported in the 12 August 2011 issue of *Science* the discovery of a stem-binding antibody that neutralized *every* H subtype. "You can't just cut it out." Basically, headless hemagglutinins fall apart.

Virologist Peter Palese's lab at the Icahn School of Medicine at Mount Sinai in New York City described a creative way around the problem in the June *Journal of Virology*. Even though people fail to make high levels of antibodies to the stem, they do make some and thus develop what's known as immunologic memory. So they reasoned that a vaccine might work if it had an engineered, chimeric hemagglutinin made from the stalk of a virus that humans had seen, triggering a robust memory response, with an "irrelevant" head that had circulated only in other species. They mimicked this chimeric vaccine in a mouse model, and it protected animals from distantly related flu viruses.

A research team at the National Institute of Allergy and Infectious Diseases has had impressive results in mice and ferrets with a different tack. The bNAbs to influenza are slow to develop in part because hemagglutinin naturally crowds the viral surface, hiding the stem regions of the protein from the immune system. Led by virologist Gary Nabel, the group described in the 4 July issue of *Nature* how it created an artificial, self-assembling nanoparticle called ferritin, an iron-storage protein, that expresses hemagglutinins at an unnatural angle, exposing their stalks. This new presentation of the protein leads to a potent bNAb response. Nabel, now chief scientific officer at vaccinemaker Sanofi, has high hopes that the days of seasonal flu shots are numbered. "We have the ability to steer the immune system back to where we want it to be," he says. **–J. C.**



Conservative thinking. Unlike the head, the stem of the influenza viral spike tolerates little change and is the target of several bNAbs.

CREDIT: G. J. NABEL AND A. S. FAUCI, *NATURE MEDICINE* 16, 12 (DECEMBER 2010) © 2010 NATURE AMERICA INC.

one day win the best of show. "It's ingenious that you'd prime with one epitope and boost with another epitope to chaperone the B cell response until the point that it's truly making a broadly neutralizing antibody," says immunologist Anthony Fauci, NIAID's director.

Burton, working with Scripps immunologist William Schief, also tracked the emergence of a bNAb, but they did so retrospectively. They started with a powerful bNAb and used genetic modeling to predict its ancestor's characteristics. Guided by what they learned, they hope to design a single immunogen that both tickles the right B cells into action *and* steers them to move from the germline antibody toward the mature bNAb. Unlike the Haynes group, Burton and Schief's team does not want to hold the immune system's hand and guide the germline B cell to make the bNAb. "Taking that too literally is likely to be asking for too much micromanagement," Schief says.

As the group explained in the 10 May issue of *Science*, a screen of massive gp120 libraries led to one that strongly bound both their putative germline antibody and the mature bNAb that evolved from it. The investigators then groomed this gp120 to contain little more than the epitope that both antibodies target. They now hope to show that they can elicit a bNAb response by "priming" the immune system with this artificial gp120, then following with a booster that contains trimer spikes in the most natural configuration possible.

Both the Burton/Schief team and Haynes's group have monkey studies under way to test their ideas. But even if they learn how to generate bNAbs, Fauci notes that a fundamental, proof-of-principle experiment has yet to happen: No one has shown that giving bNAbs to a person can prevent an infection. To that end, the Vaccine Research Center at NIAID hopes to soon launch human studies that passively give monoclonal bNAbs—which theoretically could last in the body a few months—to newborns of HIV-infected mothers and, separately, to adults at high risk of becoming infected. "Whether they're going to prevent acquisition of HIV is an open question," Fauci cautions.

Even if the bNAb strategy passes all these hurdles, years of testing will still be needed to prove that the vaccine protects people and is safe. But Fauci and many others at the forefront of the HIV vaccine search say bNAbs have brought a level of hope and common purpose that this fractious, battle-weary field has rarely, if ever, enjoyed.

–JON COHEN

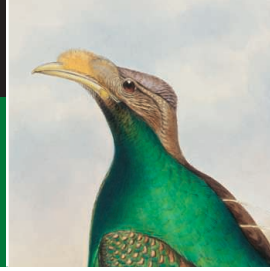
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LETTERS

edited by Jennifer Sills

Turkey's Biodiversity Funding on the Rise

THE NEWS & ANALYSIS STORIES "FRAGILE WETLAND WILL TEST TURKEY'S RESOLVE IN PROTECTING biodiversity" and "For scientists, protests morph into fight for academic freedom" (J. Bohannon, 26 July, p. 332) deserve to be set in a wider context. Turkey is covered by three global biodiversity hot spots and has 3000 endemic plant species and nearly 100 endemic vertebrates (*1*). Its wetlands lie on one of the three principal migration routes for Eurasian birds wintering in Africa (*2*). One might therefore hope for a strong financial commitment to biodiversity conservation, not least because Turkey has ratified the Convention on Biological Diversity (*3*).

We compared Turkey's biodiversity funding to other countries' for 2001 to 2008. We used newly acquired data (*4*, *5*) to expand on a recent study (*6*) from which Turkey had been excluded due to inadequate information on its conservation financing. We estimate that Turkey's funding was $13.5 million U.S. dollars (USD) annually (mean for 2001 to 2008). This level of expenditure ranks Turkey as one of the 20 worst countries in the world for funding biodiversity, alongside countries such as Republic of the Congo and Côte d'Ivoire (*6*). Indeed, Turkey's own 2007 Biodiversity Action Plan states that "the insufficiency of [financial] resources…and the ineffective use of resources...draw attention" (*7*).



Aras River in Turkey.

Such substantial underfunding represents a potential extinction risk for both local and global biodiversity, including nearly 2000 threatened endemic plant species (*1*). However, there are recent, promising changes. Turkey's 2012 and 2013 conservation budget was triple the 2004 budget in real terms (*4*, *5*). This is roughly equivalent to jumping 20% up the rankings in 8 years (from 113th to 87th out of 128 countries analyzed). Turkey had also planted more trees than any other country except Ethiopia in 2009, even if largely in a production forestry context (*4*, *8*).

The new level of funding effort thus represents one large step forward, although many more steps are needed to halt biodiversity loss (*9*). For one, we strongly encourage Turkey's government to make the unusually high 2012 and 2013 budget commitments a new baseline for coming years, pending further improvement. We must also work to increase international donor contributions to biodiversity in Turkey, which fell from $6 million USD annually in 2000 to 2001 to $0.75 million USD in 2007 to 2008 (*10*). Regardless of funding, to improve its environmental performance, Turkey will have to enforce its environmental laws rather than dismantle them (*9*).

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Waiving Concerns About Conflicts of Interest

IN THEIR POLICY FORUM "UNCAPPING CONflict of interest?" (7 June, p. 1172), S. F. Wood and J. K. Mador argue for caps on the Food and Drug Adminstration (FDA) waivers of conflicts of interest (COIs) among members of advisory committees, but they do not identify substantial weaknesses in their arguments.

A systematic study by an FDA contractor tested and rejected the hypothesis that advisers with waived and disclosed COIs vote in favor of those interests more frequently than advisers with no such conflicts (*1*). Golec *et al*. independently report similar results (*2*). If advisers with disclosed COIs vote like advisers with no such conflicts on questions such as product approvals and blackbox warnings, it is not clear how limiting the number of committee members with COIs would improve committee recommendations.

Wood and Mador claim that many able and willing experts lack conflicts, but do not mention descriptions of unsuccessful searches for COI-free advisers typically found in the FDA's COI waivers [e.g., (*3*, *4*)]. Granting more COI waivers may increase

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the FDA's access to expertise, because advisers with waived COIs have more expertise than other advisers (*5*). The FDA, however, does not report (and may not collect) sufficient data to confirm whether the reduction in waivers has affected its access to expertise.

The authors critique FDA's focus on financial ties less than 12 months old, implying that grants and contracts that ended shortly before the 1-year window still constitute COIs. In fact, federal rules define a COI in terms of whether the particular matter—e.g., the drug approval—will have a direct and predictable effect on the adviser's financial interest (*6*), regardless of the time frame. Wood and Mador also fail to acknowledge the FDA's impartiality determinations (*7*, *8*), which cover noncurrent financial ties. Caps would have value if the system were otherwise flawed, but the FDA's processes are more robust than Wood and Mador acknowledge.

Finally, the authors do not address possible indirect effects of the COI waiver cap. The FDA's division directors, who identify most advisory committee experts, might prefer that each meeting avoid surpassing the COI waiver cap. If risk-averse, they might find such a strategy sensible because FDA leadership has stated that it would be better to have no COIs—even though forgoing expert advisers with COIs might leave the FDA with less access to expertise overall (*5*).

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Response

THE IMPACT OF A FINANCIAL CONFLICT OF interest (COI) on individual decision making as part of a group is difficult to quantify, as noted by Lutter and discussed in our Policy Forum. However, because the U. S. Food and Drug Administration (FDA) is a science-based agency making critical decisions on approval and labeling of medical products, avoiding even an appearance of a COI is paramount. Indeed, public confidence depends on it. The FDA and its review divisions were quite successful in reducing the number of members of advisory committees with financial COIs, clearly demonstrating that the FDA is capable of identifying such individuals without increasing vacancy rates on the committees or reducing productivity.

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As Lutter identifies, there are indeed cases when specific experts are needed and it is necessary for the FDA to provide a waiver to allow them to serve. For example, certain pediatric specialties and some rare diseases may have few experts available who do not have a financial COI. The FDA, both in individual meetings and as a whole, was well below the previously required limits for waivers, so in these cases, waivers can and should be granted to conflicted experts.

But removing the legal limit on waivers—as was successfully done last year when there was no need to do so—raises real concerns. There was no problem to be fixed. Pressure seems to have been brought to bear on Congress and potentially on the FDA to increase the number of waivers beyond the limit, and to increase the number of advisory committee experts who have a financial interest in pharmaceutical or medical device product development.

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CORRECTIONS AND CLARIFICATIONS

Reviews: "Pivoting the plant immune system from dissection to deployment" by J. L. Dangl *et al*. (special section on Smarter Pest Control, 16 August, p. 746). In the Acknowledgments, two items were missing. Funding in the lab of J.L.D. on this topic is also supported by NSF grant IOS-0929410. B.J.S. is funded by NSF grants IOS-1146793 and BREAD-0965418 and NIH grant AI-087245. The HTML and PDF versions online have been corrected.

Reports: "Detection of a spinning object using light's orbital angular momentum" by M. P. J. Lavery *et al*. (2 August, p. 537). In the first full paragraph after equation 2, the phrase in parentheses should have appeared as "(small α, where $\sin \alpha \approx \alpha$)." The HTML and PDF versions online have been corrected.

TECHNICAL COMMENT ABSTRACTS

Comment on "Influence of HLA-C Expression Level on HIV Control"

Elisa Lo Monaco, Elisa Tremante, Priscilla Biswas, Martin P. Cranage, Donato Zipeto, Alberto Beretta, Patrizio Giacomini

Apps *et al*. (Reports, 5 April 2013, p. 87) found that high human leukocyte antigen C (HLA-C) expression favors HIV-1 control. However, as noted here, HLA-C was assessed with a monoclonal antibody (DT9) that cross-reacts with HLA-E. In the context of the available evidence, this is consistent with the idea that the two leukocyte antigens collaborate to keep the HIV-1 virus at bay.

Full text at http://dx.doi.org/10.1126/science.1241266

Response to Comment on "Influence of HLA-C Expression Level on HIV Control"

Richard Apps and Mary Carrington

Lo Monaco *et al*. propose that human leukocyte antigen E (HLA-E) and HLA-C expression levels both contribute to HIV control. The minimal, flat level of cell surface HLA-E detectable by staining with available HLA-E–specific antibodies questions a role for differential HLA-E expression in determining HIV control. Evidence remains far stronger that HLA-C expression levels as detected by the DT9 antibody specifically affect HIV control.

Full text at http://dx.doi.org/10.1126/science.1241854

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the past 3 months or matters of general interest. Letters are not acknowledged upon receipt. Whether published in full or in part, Letters are subject to editing for clarity and space. Letters submitted, published, or posted elsewhere, in print or online, will be disqualified. To submit a Letter, go to www.submit2science.org.

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MATERIALS SCIENCE

Toward Lighter, Stiffer Materials

Lightweight cellular (porous) materials are assembled from prefabricated building blocks.

Tobias A. Schaedler, Alan J. Jacobsen, Wiliam B. Carter

For hundreds or even thousands of years, humans have developed ever lighter and stronger materials, including alloys, polymers, and composites. Recently, these efforts have been joined by a different approach to lightweight materials: the introduction of carefully engineered open structure into solid materials to create cellular materials (see the figure). On page 1219 of this issue, Cheung and Gershenfeld (*1*) present a fabrication method for cellular materials that enables them to reversibly assemble cellular composite materials with tailored properties.

The properties of cellular materials are determined not only by the solid constituents but also by the spatial configuration of voids and solid—that is, the cellular architecture. The random cellular architecture of foams and aerogels results in bending-dominated deformation of the ligaments, resulting in a rapid decrease in strength and stiffness as porosity is increased (*2*). In contrast, certain ordered lattice-type cellular architectures can have nearly optimal stretching-dominated properties, resulting in materials in which the strength and stiffness scale proportionally to the solid volume fraction of the material (*3*).

The importance of architecture is illustrated readily in large, familiar structures such as buildings or wheels. The first wheels were made out of solid stone or wood and had no notable porosity. In contrast, modern bicycle wheels have a sophisticated architecture, in which more than 95% of the material has been replaced with air. Excellent strength and stiffness is achieved despite the light weight by loading the spokes in tension, where their performance is stretch-dominated, not in compression, where they would buckle and bend easily. The same concept is used to reduce the mass of materials in many weight-critical applications; for example, the cores of surfboards and rotor blades are not solid but made from foam and honeycomb, respectively.

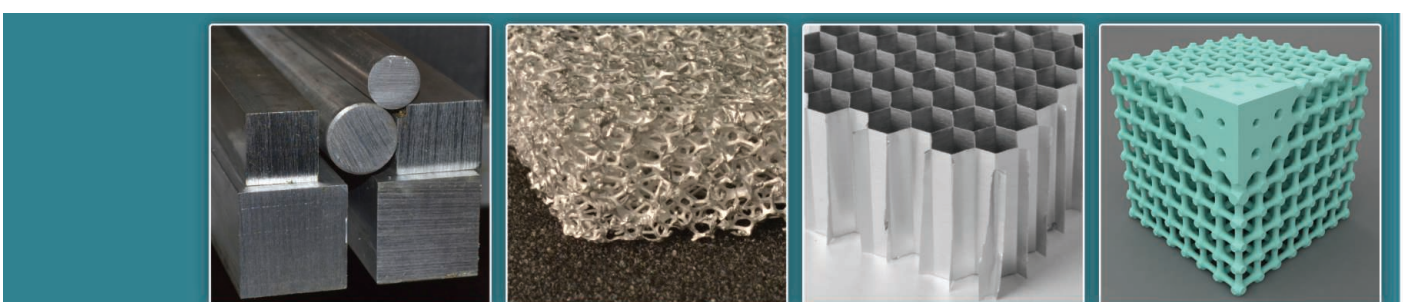
Architecture thus provides an array of additional degrees of freedom when designing a material. In lattice materials, the unit cell configuration and symmetry, ligament size and shape, and node topology can be altered independently (*4*). Studies of ultralightweight microlattice materials have shown that by independently changing these different architectural parameters, conventionally linked properties such as density, stiffness, and strength can be decoupled (*5*).

One advantage of cellular materials is that a well-known material can be used as the solid constituent and, within physical limits, its architecture can be adjusted to achieve properties needed for a particular application. Also, whereas the design of alloys or polymers is generally still hindered by limited scientific understanding and computational power, that of cellular materials is more tractable: Cellular architecture and suitable constituent solid materials can be combined using known structural engineering principles (*6*).

By varying cellular architecture, material properties can be altered throughout a part in such a way that the target application is maximally enabled. Methods such as additive manufacturing and three-dimensional (3D) printing offer the opportunity to tailor properties to location-specific requirements. Cheung and Gershenfeld use this concept to tune the global deformation properties of their cellular composite materials by changing the placement of different building blocks. Structures with the same lattice geometry either axially compress or buckle and tilt sideways under identical constraints and loading, depending on the relative placement of rigid and flexural components.

Powerful computational tools to optimize structures for mechanical efficiency (*7*) allow the most structurally efficient and lightweight architecture for a complex part and load case to be computationally determined, but today's manufacturing capabilities still impose limits on what can be made. New fabrication routes for cellular materials are exemplified by 3D printing, but considerable progress must still be made to enhance the scale, throughput, reliability, and palette of materials available.

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Adding architecture to materials. Traditionally, the properties of materials have been altered by varying the microstructure and production process. Changing the cellular architecture, i.e., the spatial configuration of voids and solids, is a powerful additional route to desirable materials properties. By varying architecture locally within a cellular material, properties can be tuned to location-specific requirements, as exemplified by the model structure on the right (*11*). Cheung and Gershenfeld report a method for reversibly creating an ordered cellular architecture based on prefabricated building blocks.

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Cheung and Gershenfeld's approach of assembling building blocks circumvents some of these issues, because the building blocks (consisting of a unidirectional carbon fiber composite) are prefabricated with conventional methods that are optimized to achieve the best possible axial properties (*8*). By assembling these building blocks instead of creating material in situ (e.g., by sintering or melting powders), these excellent properties can be translated to a cellular material while retaining many of the benefits of additive manufacturing. The building blocks can be mass-produced and then assembled to fill arbitrary structural shapes, with a resolution prescribed by the building block scale.

The building block assembly still needs to be automated, and it remains to be seen whether the approach reported by Cheung and Gershenfeld will be competitive with other methods. Commercial methods of fabricating elaborate cellular materials and structures (stereolithography, selective laser sintering, electron-beam melting, etc.) are still slow and expensive relative to common industrial manufacturing methods, but faster, scalable methods such as self-propagating photo-polymerization (*9*) are emerging, and self-assembly techniques such as DNA origami (*10*) on the nanoscale could one day be used to assemble larger building blocks. The resulting materials could find applications in the automotive, aerospace, sporting, and consumer goods industries, leading to improvements in fuel efficiency, performance, and convenience.

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EVOLUTION

What, Where, and When?

Alfred Russel Wallace's science of distribution provided the foundation of biogeography.

Sandra Knapp

Alfred Russel Wallace, whose contributions to science we celebrate this year, the 100th anniversary of his death, is probably best known for his role in articulating evolution by natural selection with Charles Darwin in the mid-19th century. But important as that was, it was his unique field-oriented perspective that gave birth to a whole new way of looking at the world. In his two-volume *The Geographical Distribution of Animals* (*1*), Wallace broke new ground by setting patterns of distribution in an evolutionary context and insisting on the necessity for comparative data across all of life (see the first figure). He can rightly be hailed as the founder of biogeography, a field that is today more important than ever as concerns mount over the fate of biodiversity.

Wallace's conceptualization of evolution by natural selection had a distinctly geographical slant. In 1855, he wrote that "every species has come into existence coincident both in space and time with a pre-existing closely allied species" (*2*); in other words, diversification has a geographical as well as time dimension. He used his careful observations in Southeast Asia to pinpoint the sharp division between the Indian and Australian faunas at the Lombok Strait (see the second figure) (*3*). Today we call that division the Wallace Line and understand that it relates to two great plates of the Earth's crust that are adjacent now, but were not so in the distant past. But his concern for geography began earlier. While collecting in the Amazon, he sent letters back to London urging explorers to more accurately record where their specimens were collected (*4*).

His zoogeographical regions of the world (see the first figure) (*1*) are still used today. We talk about the Nearctic, Palaearctic, Neotropical, Ethiopian, Oriental, and Australasian regions, and many of the great natural history museums are organized on these principles. Although these regions have been revised and refined, the current view (*5*) is very like that Wallace presented in the late 19th century. But considerable debate (*5*, *6*) remains about just how scientists should classify biotic areas. Wallace aimed for a global view, but at different scales and different levels of detail (*7*), geography is as complicated as the organisms that inhabit it.

There was a lot Wallace did not know. For example, plate tectonics furnished the explanation of previously enigmatic patterns of distribution, such as the presence of large flightless birds (ostriches and their relatives) all around the Southern Hemisphere. But he did realize that life and Earth had evolved together and that we could only understand how this occurred by looking at large data sets gathered across all organisms.

The "science of distribution" has come a long way from being mainly a description of where organisms occur. Today, biogeography is a synthetic discipline that seeks to understand how Earth's history has influenced the life it holds and that is increasingly used to effect biodiversity conservation in the face of threats from environmental change. Knowledge of range sizes underpins the IUCN Red List (*8*), and comparison of geographic ranges is used to discover "hotspots" of endemism—places with great concentrations of species that occur nowhere else and are targets for conservation (*9*).

Islands and their biota featured prominently in the development of biogeography; as small areas with obvious edges, islands are ideal for exploring distributional questions. Wallace's own book *Island Life* (*10*) was subtitled "or the Phenomena and Causes of Insular Faunas and Floras, Including a Revision and Attempted Solution of the Problem of Geological Climates." Island biogeography focused study not only on the patterns of species distribution, but also on the ecological factors that governed the assembly of species diversity on tractable island systems.

The 1980s emphasis on repeatability and method in systematics gave rise to cladistic biogeography (*11*). This, coupled with attempts to understand more complex continental distribution patterns, gave biogeography a pattern-focused, rather than ecological, slant. Much ink was used arguing (*12*) the relative roles of dispersal (chance movement of organisms from centers of origin) and vicari-

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Science of distribution. Many of the zoogeographical regions defined by Wallace in this map (*1*) are still in use today.

ance (movements of areas of the Earth) in distribution patterns we see today. Interpretation of fossils and the key role of paleontology in the understanding of biogeographic patterns were touchstones in these debates.

Interest in a variety of scales of geographical pattern meant that methods were developed for each. The advent of DNA sequencing and the ability to quantify allele frequencies in populations gave birth to phylogeography, and additional levels of complexity were revealed, but disputes (*13*) as to which method is best are as divisive as were the vicariance versus dispersal debates of the 1980s. Next-generation DNA sequencing looks set to further expand this part of biogeography (*14*), adding a further scale dimension to the biology of geography.

The use of molecular sequence data in phylogeny reconstruction also reinvigorated the vicariance/dispersal wars. Because dated molecular phylogenies revealed ages of taxon splits much younger than could be accounted for by simple vicariance, long-distance dispersal of organisms became a stock explanation for unexpected patterns. However, many outside the field of molecular phylogenetics fail to appreciate that these dates, calculated with a "molecular clock" and calibrated with fossils, are minimum dates and come with big error bars. Vicariance is fighting back, too, with the advent of molecular panbiogeography (*15*), an attempt to reconcile molecular phylogenetic data with a view of geography as tracks and nodes related to tectonic events.

The ever more explicit integration of time in biogeography has been a hallmark of its development. As knowledge about the timing of geological events has increased, simple hypotheses of how distributional patterns of organisms relate to these events must be refined. The refugium hypothesis for the origin of Amazonian diversity is a case in point. The idea that drying cycles over the past ~3 million years drove the retraction of species ranges into refugia from where they subsequently spread in wetter times was attractive, but hotly disputed. More data from both biology and geology add depth and nuance to the story (*16*). The need for a comparative biogeography (*17*) is obvious here; stories from single groups of organisms cannot be extrapolated to explain geographical phenomena at an area scale.



Sharp division. Wallace noticed a complete difference in the bird faunas along what is today called the Wallace Line. Birds of paradise, of which Wallace's standardwing [Plate 52 in (*19*)] is an example, are found only to the east of the line, in the Australian region.

What has not changed since Wallace's day is the need for well-documented material—whether specimens from museums used to plot species occurrences or sequence data used to generate phylogenetic trees—on which to base comparative hypotheses. This is where collections amassed by previous generations of naturalists like Wallace are necessary, but not sufficient. Many older specimens lack useful geographic information; I have seen collections labeled New World or Brazil, hardly useful for much beyond the question of what. New, properly documented observations are critically important for hypothesis testing.

Consortia like the Global Biodiversity Information Facility (*18*) aim to facilitate access to dispersed museum data, but a look

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at the data reveals huge bias, with diversity highest in the north temperate zones and most data points as birds. We know intuitively that biodiversity is not highest in Europe and the United States, and that most organisms are not birds. Thus, in addition to the robust debates about theory and methods that are part of today's biogeography, we must also pay attention to improving and adding to the underlying data and not neglect it in favor of studies that reuse the same data from single organism groups.

Today, the science of biogeography is more important than it ever has been, as concerns mount over the fate of biodiversity (*10*). As a comparative endeavor, it has the potential to shed light on how life and Earth have evolved together. But it is still necessary to heed Wallace's admonition: "None of these questions can be satisfactorily answered till we have the range of numerous species accurately determined" (*4*). Methods change and theories abound in this vibrant branch of science, but accurate data for comparison are critical for the holistic understanding of the relationships between Earth and its biota that biogeography seeks.

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IMMUNOLOGY

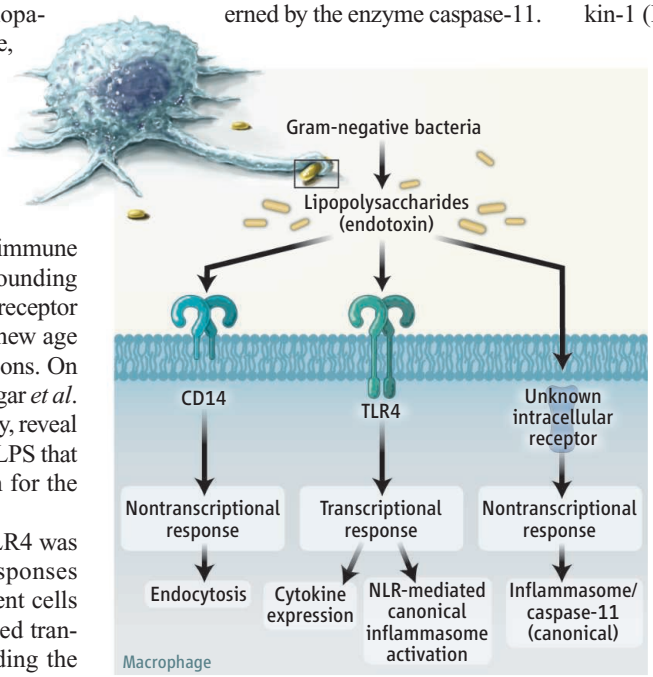
Sensing Endotoxins from Within

Macrophages respond to bacteria through a protein complex that promotes inflammation when activated by internalized bacterial endotoxin.

Jonathan C. Kagan

The human innate immune system identifies Gram-negative bacteria by recognizing lipopolysaccharides (LPS), components of the microbial cell wall (*1*). This detection triggers massive inflammatory responses that help eradicate infections, but may also result in immunopathology if regulated improperly. Hence, LPS is also referred to as endotoxin. More than a century after its discovery, the molecular basis for the inflammatory activity of endotoxin was finally revealed by the discovery that Toll-like receptor 4 (TLR4) induces innate and adaptive immune responses to LPS (*2*). TLR4 is the founding member of the mammalian Toll-like receptor family, and its discovery heralded a new age in the study of host-microbe interactions. On pages 1250 and 1246 of this issue, Hagar *et al.* (*3*) and Kayagaki *et al.* (*4*), respectively, reveal the existence of cellular responses to LPS that do not depend on TLR4. The search for the new LPS receptor can now begin.

For years, it was assumed that TLR4 was solely responsible for cellular responses induced by LPS (*5*, *6*). TLR4-deficient cells are defective for all classically defined transcriptional responses to LPS, including the expression of inflammatory cytokines and interferons (*7*). However, LPS can also induce nontranscriptional cellular responses, such as autophagy, endocytosis, phagocytosis, and oxidative bursts (*8*–*11*). Hagar *et al.* and Kayagaki *et al.* add to this list of atypical responses to LPS, by showing that LPS activates the formation of an atypical inflammasome governed by the enzyme caspase-11.



Sensing lipopolysaccharides. Macrophages respond to Gram-negative bacteria by activating transcriptional and nontranscriptional immune responses. Some of these responses are handled by protein complexes called inflammasomes. An intracellular sensor for lipopolysaccharides was revealed, but its identity has yet to be determined.

Inflammasomes are protein complexes that are assembled in the cytosol of macrophages in response to a variety of extracellular stimuli (*12*). The best-defined function of inflammasomes is to promote the processing and secretion of inflammatory cytokines of the interleukin-1 (IL-1) family. At the center of the best-characterized inflammasomes is the enzyme caspase-1, which cleaves the precursor of IL-1 in the cytosol of macrophages. Cleaved IL-1 family members are then secreted to induce inflammation. A second class of inflammasomes also requires caspase-11 to promote IL-1 cleavage (*13*). These noncanonical inflammasomes are activated by intracellular bacteria and contribute to the phenotypes associated with sepsis. How these noncanonical inflammasomes are activated remains unclear.

Hagar *et al.* and Kayagaki *et al.* recognized that several species of Gram-negative bacteria can activate caspase-11–dependent IL-1 secretion (*13*). Thus, a molecule common to Gram-negative bacteria must be responsible for activating caspase-11. Both research groups show that LPS is the molecule of interest. For example, Hagar *et al.* show that when transfected into macrophages, cell lysates derived from Gram-negative bacteria, but not Gram-positive bacteria (which contain no LPS), can

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activate caspase-11. This effect was insensitive to proteases and nucleases, thus ruling out the actions of any protein or DNA/RNA species in the bacterial lysate. However, the effect was lost when the lysate was treated with ammonium hydroxide, a chemical that inactivates LPS. Both Hagar *et al*. and Kayagaki *et al*. showed that transfection of pure LPS into macrophages was sufficient to activate caspase-11.

Interestingly, both Hagar *et al*. and Kayagaki *et al*. found that to activate this noncanonical inflammasome, LPS must be in a complex with transfection reagents, or some other means of delivering LPS into the intracellular compartment(s) of the cell. Because TLR4 senses LPS in the extracellular environment, this observation suggested that TLR4 was not responsible for activating caspase-11. Indeed, macrophages lacking TLR4 retained the ability to activate caspase-11 in response to transfected LPS. Thus, an additional LPS sensor must be present within cells. These studies provide the mandate to begin the search for this protein, and understand its function in host-microbe interactions and inflammation.

Although the identity of this new LPS sensor remains unknown, the studies by Hagar *et al*. and Kayagaki *et al*. provide some clues as to where this protein may reside in the cell. That LPS must be delivered into the cell suggests that the LPS sensor is present in an intracellular location. Hagar *et al*. showed that LPS can activate caspase-11 if it is in a complex with the Gram-positive bacteria *Listeria monocytogenes*, but only if the bacteria can enter the cytosol of the host cell. This indicates that the LPS sensor is a cytosolic protein. However, both studies also used the B subunit of cholera toxin as an "LPS delivery vehicle." Cholera toxin B follows a retrograde vesicular trafficking pathway from the plasma membrane to the lumen of the endoplasmic reticulum, but never accesses the cytosol (*14*). This raises the intriguing possibility that the LPS sensor does not reside in the cytosol, but instead in an intracellular compartment. Future genetic and cell biological studies are necessary to elucidate this fascinating new LPS sensory system.

The identification of a cellular response to LPS that does not require TLR4 draws parallels with recent work on other nontranscriptional responses to LPS. For example, the ability of LPS to induce endocytosis is controlled not by TLR4, but rather by the protein CD14 (*15*). Thus, a theme is emerging whereby TLR4 controls all transcriptional responses to LPS, but at least some of the equally important nontranscriptional responses are controlled by receptors other than TLR4 (see the figure). A future challenge will be to define not only the regulators of this new LPS response, but also how all responses to bacteria are interconnected in space and time.

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PHYSICS

Opportunities Knock with a More Stable Optical Clock

Improvements in the stability of atomic clocks could enable local gravity measurements and tests of fundamental physics.

Helen S. Margolis

Recently, there has been rapid progress in the development of a new generation of optical atomic clocks that operate at frequencies around five orders of magnitude higher than their microwave predecessors. Because the instability of an atomic clock is inversely proportional to its operating frequency, optical clocks offer the prospect of achieving substantial improvements in measurement precision, potentially at the level of 1 part in 10^{18} for averaging times of a few hundred seconds. On page 1215 of this issue, Hinkley *et al*. (*1*) report an important step toward reaching this goal: a comparison between two ytterbium optical lattice clocks that demonstrates unprecedented clock instability of 1.6 parts in 10^{18} for an averaging time of 7 hours.

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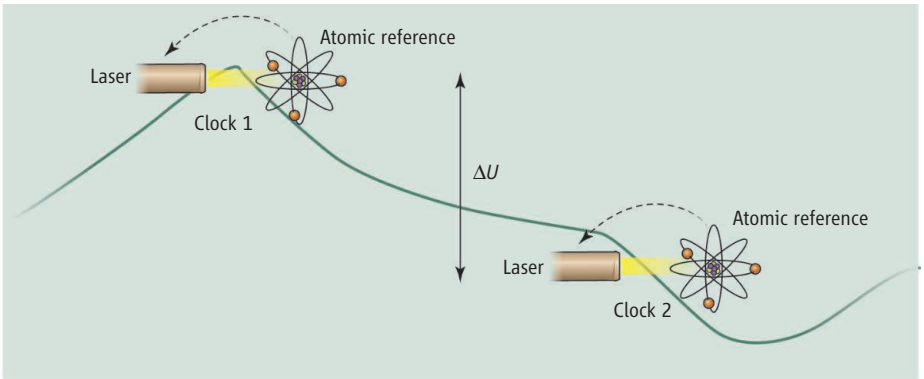
Optical atomic clocks are based on ultrastable lasers that are stabilized to narrow atomic absorption features (clock transitions) in the optical region of the electromagnetic spectrum. Two different types of atomic reference are being studied as candidates for optical clocks, based on clock transitions in either single laser-cooled trapped ions (*2*) or thousands of laser-cooled atoms trapped in an optical lattice (*3*). The optical lattice type is advantageous with respect to theoretically achievable instability, because a larger number of atoms yields an improved signal-to-noise ratio in the measurement of the atomic absorption frequency.

Despite this theoretical advantage, the demonstrated stability of optical lattice clocks was, until recently, similar to that of optical clocks based on single ions, mainly because of technical limitations imposed by the noise of the clock laser used to probe the narrow absorption feature. Because a measurement cycle includes time for laser cooling and state preparation of the atoms, the difference between the clock laser frequency and the atomic absorption frequency is measured only during a fraction of the complete cycle time. This periodic sampling of the clock laser noise degrades the achievable stability of the clock, a phenomenon known as the Dick effect (*4*).

When comparing two optical lattice clocks, the Dick effect can be eliminated by probing the two clock transitions synchronously with the same clock laser (*5*). Although this procedure can be useful in reducing the averaging times required to evaluate the performance of the clock, it does not improve the instability of each individual clock as a timekeeping device. Other approaches to minimizing the Dick effect, such as reducing the instability of the clock laser and minimizing the dead time in the measurement cycle, are required. Key to the new results reported by Hinkley *et al*. is their

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Clock-based geodesy. According to general relativity, two identical clocks placed in gravity potentials that differ by ΔU will be observed to differ in frequency by $\Delta f/f = \Delta U/c^2$, where c is the speed of light in vacuum. High-resolution measurements of the gravity potential made by comparing transportable optical clocks would complement the data obtained from satellite missions such as GOCE (Gravity Field and Steady-State Ocean Circulation Explorer), which provide global coverage but give values that are spatially averaged over length scales of about 100 km.

earlier development of a clock laser with a frequency instability of 2 to 3 parts in 10^{16} for averaging times of a few seconds (*6*).

The experiments performed by Hinkley *et al*. compared two clocks located in the same institution. Optical fiber links enable clocks separated by hundreds of kilometers to be compared with high precision (*7*), but such comparisons are complicated by the effects of general relativity, which tells us that the frequency of a clock is affected by the local gravity potential it experiences. For a clock comparison with a precision of 1 part in 10^{18}, the gravity potential difference must be known with an accuracy of about 0.1 $m^2\ s^{-2}$, which corresponds to about 1 cm in height at Earth's surface. This not only represents a substantial improvement on the current state of the art, but also requires the evaluation of time-varying effects such as those caused by tides (*8*).

Some time-varying effects are predictable, but others are not, and the latter will set fundamental limits to the use of clocks as timekeepers. Viewed from another perspective, however, these effects present an opportunity: Highly stable optical clocks could be used to measure gravity potential differences between well-separated points with high sensitivity and high temporal resolution (see the figure). Indeed, plans have already been made to demonstrate the benefits that optical clocks could bring to the field of geodesy by carrying out proof-of-principle experiments of this type (*9*).

Optical clocks with instability of 1 part in 10^{18} also offer opportunities to test fundamental physical theories with very high sensitivity. One example is the search for temporal and spatial variation of the fine structure constant α, which is predicted by theories that aim to unify the four fundamental forces of nature. The best current constraints on present-day variation in α already come from comparisons between different optical clocks (*10*), and as the measurement precision achievable with the clocks improves, increasingly more sensitive tests will be possible.

Stability, however, is not the only important property of an optical clock. Accuracy—the uncertainty in correcting for systematic effects that shift the unperturbed frequency of the clock transition—is even more critical for certain applications, such as an anticipated future redefinition of the SI second (*11*). The record for accuracy is currently held by a trapped ion optical clock (*12*), with Hinkley *et al*. having yet to fully evaluate the systematic uncertainties of their optical lattice clocks. What is certain, however, is that the unprecedented instability they have demonstrated will ease this task by reducing the averaging times needed to characterize each systematic effect with high precision.

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CANCER

Circulating Tumor Cells

Vicki Plaks, Charlotte D. Koopman, Zena Werb

Much remains to be learned about CTCs and their clinical potential as biomarkers and therapeutic targets.

The major cause of cancer-associated mortality is tumor metastasis, but our understanding of this process is far from complete. During successful dissemination, tumor cells invade the surrounding tissue of the primary tumor, intravasate into blood and lymphatic vessels, translocate to distant tissues, extravasate, adapt to the new microenvironment, and eventually seed, proliferate, and colonize to form metastases. Because dissemination mostly occurs through the blood, circulating tumor cells (CTCs) that have been shed into the vasculature and may be on their way to potential metastatic sites are of obvious interest (*1*). Here we discuss what is known about CTCs, and suggest future research directions that may help realize their clinical potential.

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The presence of CTCs in cancer patients was first detected in 1869 (*2*). Numerous studies in the past decade have shown that CTCs may be used as a marker to predict disease progression and survival in metastatic (*2*–*4*) and possibly even in early-stage cancer patients (*5*). High CTC numbers correlate with aggressive disease, increased metastasis, and decreased time to relapse (*1*). Moreover, CTCs can initiate metastasis in a xenograft model (*6*). If CTCs are indeed a source of metastatic cells, they could become an

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integral part of tumor staging criteria, which are currently focused on the primary tumor. Because blood collection is simple and minimally invasive, CTCs could be used as a real-time marker for disease progression and survival. CTCs also have the potential to guide therapeutic management (*7*), indicate therapy effectiveness or necessity, even in the absence of detectable metastases, and offer insights into mechanisms of drug resistance. They could be used as a surrogate endpoint marker in clinical trials (*4*), but could also become a treatment target (*7*). Despite this great potential, the use of CTCs faces many hurdles (see the figure).

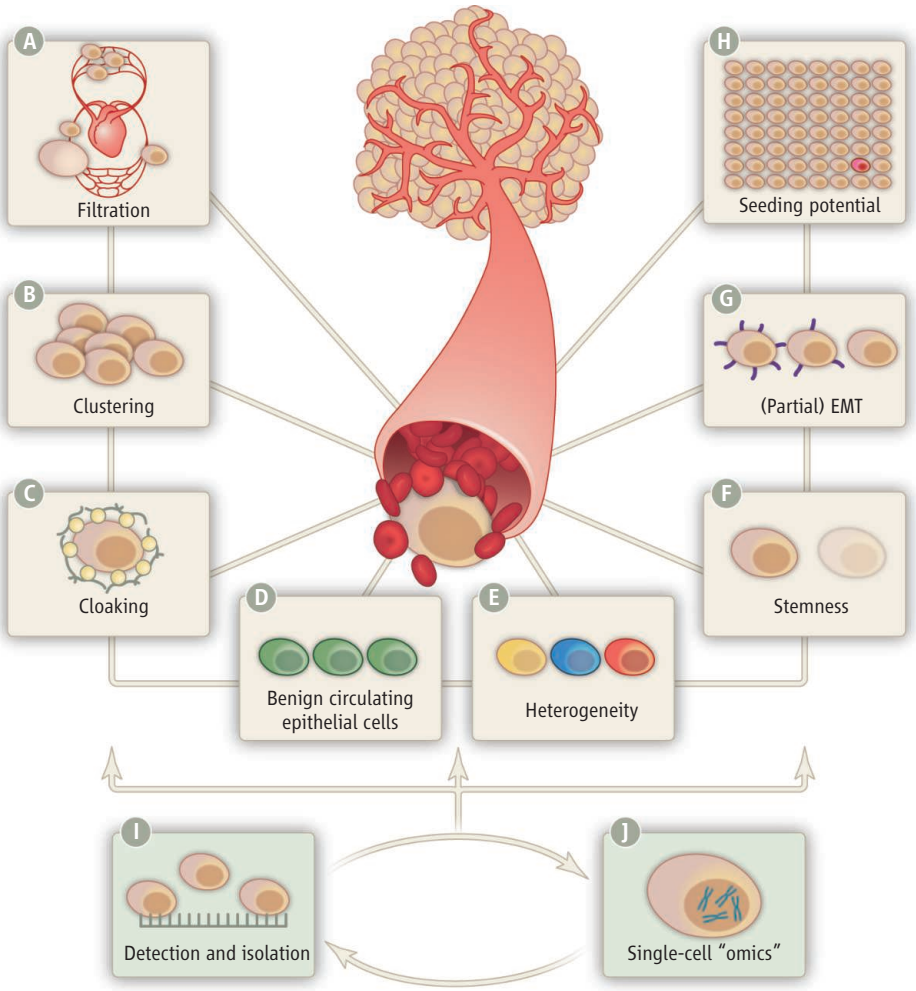
CTCs have a diameter that is three to four times as large as the bores of capillaries in distant organs, so they would be expected to become trapped there (*1*, *8*). That CTCs can be detected in the blood implies that only extremely small and/or plastic CTCs can keep circulating. And because some CTCs circulate as microclusters (*9*), these would likely also lodge in capillaries. Thus, it is unclear whether actual "circulating" tumor cells are indeed the source of metastases. Based on these points, it would be logical to assume that variations exist in the spatial and temporal distributions of CTCs within the circulation. Indeed, most solid malignancies have typical patterns of metastasis according to the localization of the primary tumor, suggesting at least partial filtration of CTCs. Thus, the site of blood collection for CTC detection may be critical. If CTCs need to be collected from various sites according to cancer type, blood sampling may not be as minimally invasive. Adding to this is the current requirement of large quantities of blood for CTC isolation and detection. Extracting blood from vessels draining the tumor may thus not be feasible and calls for the development of CTC detection devices that can handle small sample volumes. However, this poses an additional problem, because CTCs are extremely rare (*7*). For example, only 1.43% of patients with progressive breast cancer had >500 CTCs per 7.5 ml of blood (*6*). Moreover, lymphatic spread is still poorly understood (*8*), but could also be a route for tumor cell dissemination. CTCs may also be difficult to detect because they can become cloaked by platelets or by coagulation factors, thereby shielding them from the immune system. Indeed, high platelet count (thrombocytosis) is associated with poor prognosis in many cancers. Thus, a potentially metastatic subpopulation of CTCs may be currently undetectable.

Not all CTCs may be clinically relevant. Patients with various benign inflammatory colon diseases also harbored viable circulating epithelial cells detected by current CTC assays, whereas healthy subjects did not (*10*). Additionally, in a mouse model of pancreatic cancer, CTCs were found in the blood before the appearance of a primary tumor (*5*). Thus, current CTC assays are limited in distinguishing between cancer cells, noncancerous tumor components, and benign cells.

CTCs may be shed from different locations within tumors, which are heterogeneous in nature, and even from metastases. Indeed, frequently there is a clear discrepancy in gene expression between primary tumors and CTCs, as well as heterogeneity within the CTC population (*7*, *11*, *12*). It may become possible to identify the tissue of origin of CTCs by using expression profiling to detect organ-specific metastatic signatures. This would help to localize small metastatic lesions and to guide further diagnostic and therapeutic strategies.

Cancer-associated traits in some cancers have been traced to so-called cancer stem cells (CSCs). The traits that define CSCs, i.e., self-renewal, tumor-initiating, motile, invasive, and heightened resistance to apoptosis, are also instrumental for metastasis (*1*, *13*), implying that, in cancers that follow the cancer stem cell model, CTCs with high metastatic potential might be CSCs.

There is an ongoing discussion on whether tumor cells undergo epithelial-mesenchymal transition (EMT) during dissemination, resulting in a more mesenchymal or even more stem cell–like phenotype. However, current CTC detection methods mostly use the epithelial marker epithelial cell adhe-



Hurdles and solutions in CTC research. Biophysical factors that may diminish the detection of CTCs include (**A**) filtration of large CTCs in smaller capillaries, (**B**) clustering of tumor cells that lodge in capillaries, and (**C**) cloaking of CTCs by platelets or coagulation factors. Biological factors that likely complicate the detection and isolation of clinically relevant populations of CTCs that currently rely on epithelial markers include (**D**) the presence of benign circulating epithelial cells, (**E**) the large heterogeneity among CTCs, (**F**) the possible stemness of a subpopulation of CTCs, (**G**) the (partial) epithelial-mesenchymal transition (EMT) that some CTCs undergo during dissemination, and (**H**) the unclear seeding potential of detected CTCs. Future research should use technologies focused on (**I**) improving the detection and isolation of CTCs, and (**J**) single-cell "omics."

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sion molecule (EpCAM), which may underestimate CTC number and potentially miss a critical subpopulation (*1*, *7*). Although it has yet to be shown in spontaneously arising cancers in vivo, EMT can induce non-CSCs to enter a CSC-like state, generating CSCs de novo (*1*, *13*). However, the role of EMT in enabling metastatic dissemination is yet to be fully proven and may only operate in a fraction of cancer cells that are in close contact with adjacent reactive stroma (*1*). Present at the tumor edges, these cells may dislodge and become blood borne, i.e., CTCs. If only CTCs that undergo EMT are those with self-renewal capability and proliferative potential essential for macroscopic metastases (*13*), markers for metastatic CTCs should include EMT markers. Indeed, in many tumors, carcinoma cells exhibit a partial mesenchymal state (*1*, *9*), a phenotype absent from normal tissues (*1*). Still, it remains to be determined what fraction of CTCs lose some or all EpCAM expression and undergo (partial) EMT and whether these (or any) CTCs have increased metastatic seeding potential or heightened resistance to systemic therapy and therefore greater prognostic value. It is also unknown whether tumorigenic and nontumorigenic cells differ in their capacity to circulate in cancers that follow the cancer stem cell model. Thus, the overall relationship between CSCs and CTCs remains unclear.

That some CTCs are undetectable and not all detected CTCs have metastatic potential indicates that CTC enumeration is not a good marker for disease staging and prognosis. Instead, it is instrumental to design biomarkers based on the gene sets and genomic profile of CTC subsets that predict homing and colonization to specific distant metastatic sites or even sites of primary tumor origin. Advanced CTC analysis is being made possible by constant technical improvements in CTC detection and isolation (*7*), although there are still unresolved issues, specifically the need to standardize detection assays (*12*).

The development of single-cell analyses that can detect gene expression in individual CTCs has revealed interesting data, such as the finding of human epidermal growth factor receptor 2 (HER2)–positive CTCs in HER2-negative breast cancers (*11*). Such studies have expedited clinical trials on CTCs and indeed, the numerous ongoing trials are indicative of the vast interest in these cells. Recent genomic analysis of CTCs has detected single-nucleotide and copy-number variations generally accepted as driving forces in cancer (*14*). However, CTC genomics is still in its infancy, mainly due to a lack of technologies capable of isolating sufficient numbers of CTCs to analyze somatic mutations (*14*, *15*), and the lack of suitable material with which to compare results due to CTC heterogeneity.

The potential clinical value of CTCs is clear: Early detection and treatment of metastatic spread are key for disease outcome, and CTCs offer the ability to target metastasis in real time. Although CTCs are not yet proven to be the metastatic cells, there is no evidence that they are incapable of being so. However, a simple enumeration of CTCs without molecular characterization may lead to wrongful clinical assumptions and consequences. Elucidating CTC biology will also help standardize detection and isolation of the potentially metastatic subpopulation of CTCs. The next frontier in the CTC field is their characterization using the constantly improving single-cell "omics" techniques (*16*). This will ultimately determine the clinical value of CTCs as biomarkers and therapeutic targets.

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PHYSICS

Cold Atom Cosmology

The emergence of density fluctuations in a cloud of interacting cold atoms shows characteristic aspects of the evolution of the early universe.

Jörg Schmiedmayer[1] and Jürgen Berges[2]

At first sight, cold atoms and cosmology could not be more different; they are characterized by vastly different physical scales in energy, length, and time. On page 1213 of this issue, Hung *et al*. (*1*) report on the observation of acoustic oscillations in the time evolution of an ultracold quantum degenerate gas. This suggests that similar fundamental physics principles govern aspects of their nonequilibrium evolution.

Cosmology is time evolution. The history of the universe is imprinted on deviations from thermal equilibrium. Temperature fluctuations in the cosmic microwave background radiation are a prime example (see the figure). Analysis of these angular fluctuations has led to high-precision measurements of cosmological parameters. The increase in the fluctuation amplitude on angular scales of a degree or less is related to the phenomenon of Sakharov oscillations (*2*), where synchronously generated sound waves alternately compressed and rarefied regions of the primordial plasma. That the phases of all the acoustic oscillations were equal at some point in time during the evolution of the early universe can be understood as a result of a period of superluminal expansion or inflation (*3*).

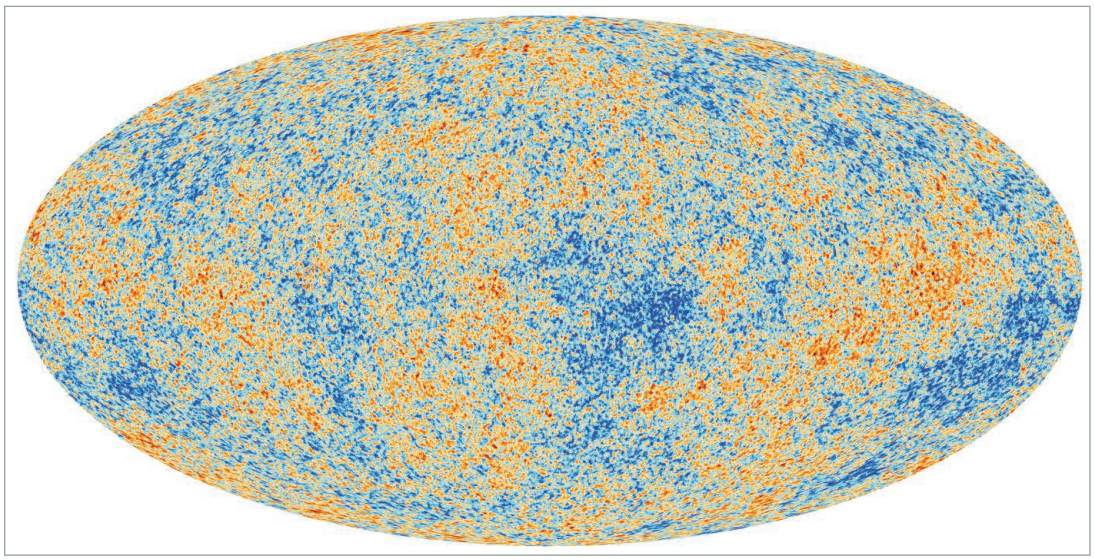
Ultracold quantum gases provide a unique opportunity for studying nonequilibrium quantum systems. Ensembles of trapped atoms are almost perfectly isolated from the environment, and their coherent quantum evolution can be probed in detail on experimentally accessible time scales. The tunability of parameters like interaction strength, temperature, density, and dimensionality supported by powerful manipulation techniques allows the realization of many different relevant physical situations.

Hung *et al*. start from a quantum degenerate sample of cesium atoms in a highly oblate trap. The atomic sample forms an almost purely two-dimensional superfluid, tens of micrometers wide and only a few hundred

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Universal fluctuations. Temperature fluctuations in the cosmic microwave background radiation as measured by the Planck satellite. The fluctuation amplitude on small angular scales is related to the phenomenon of Sakharov oscillations.

nanometers thick at a temperature of 10 to 15 nanokelvin. Abruptly changing the atom-atom interaction strength takes the system out of equilibrium. The ensuing evolution of the nonequilibrium state shows two aspects. On long time scales (50 ms), the system adjusts its overall density profile to the new interaction energy. On shorter time scales (a few ms), density fluctuations in the cloud change dramatically. These emerging fluctuations are interpreted as Sakharov oscillations (*2*), created by the sound waves generated in the interaction quench, which then interfere as time evolves.

The speed of sound in the superfluid relates the time and length scales of interference, and Sakharov oscillations should occur only within the sound cone; outside waves do not overlap and thus do not interfere.

Such a horizon was recently observed in a different experiment studying interfering one-dimensional superfluids (*4*). Splitting a single one-dimensional superfluid into two identical systems initiated a nonequilibrium evolution of growing fluctuations in the phase, which led to decay of the initial phase coherence between the two split systems over time. The measured phase correlation function revealed that the final fluctuating state emerged locally and spread throughout the system with the speed of sound. This sound cone is in close analogy with the light cone discussed in relativistic field theories.

The appearance of similar phenomena in such vastly different settings is reminiscent of the idea of building an analog quantum simulator of the inaccessible system of study, like the early universe (*5*). Although it is far-fetched to expect the full complexity of a high-energy quantum field theory to be implemented on a degenerate quantum gas, doing so is not necessary. This relies on an important property encountered in quantum field theory: The successive inclusion of quantum corrections on different characteristic scales may be viewed as a coarse graining procedure, which finds its mathematical formulation in the theory of the renormalization group (*6*). For many macroscopic quantities, this leads to a loss of details about the underlying microscopic description. Subsequently, different systems can have similar or even the same low-energy effective theory for the quantities of interest.

This behavior is connected to the phenomenon of universality, which is well understood in thermal equilibrium. A famous example concerns scaling properties of continuous phase transitions. Near these transition points, the characteristic physics becomes scale independent and the same universal scaling exponents occur in different systems if general properties such as symmetries, dimensionality of space, or number of field components coincide. In quantum or statistical field theory, the scale invariant properties are described as renormalization group fixed points.

Similar considerations may apply also to nonequilibrium dynamics in many diverse areas of physics, ranging from the inflationary universe to complex quantum systems in condensed matter physics. For instance, inflationary models typically involve a matter field that was coherently excited out of its ground state. Its relaxation can exhibit nonequilibrium instabilities during preheating (*7*), a period of rapid entropy production leading to a prethermalized state (*8*). For the former, there are suggestions to observe similar phenomena in quantum gases (*9*). The latter predicts that thermal-like properties can emerge far from equilibrium, a phenomenon also demonstrated in an ultracold quantum gas (*10*).

An example of universality far from equilibrium, governed by nonthermal fixed points, concerns infrared scaling properties, which are predicted for inflationary models (*11*), as well as ultracold Bose gases (*12*). The associated universal phenomena leading to nonequilibrium Bose condensation (*13*), which occurs even far above the critical energy for the corresponding equilibrium transition temperature, may also be directly measured using ultracold atoms.

Finding physical implementations of gauge theories in atomic setups (*14*–*16*) may further boost our abilities of addressing problems relevant for cosmology or particle physics that are often difficult to study.

Selecting cold atom systems with suitable Hamiltonians offers the prospect to learn at least qualitatively about otherwise inaccessible phenomena. For universal aspects, this gains more predictive power and, despite the vast differences in characteristic scales, we may indeed learn from table-top experiments with cold atoms quantitative aspects about the dynamics during the very early stages of our universe.

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INTRODUCTION

The Future Is Now

IN THE MORE THAN 100 YEARS SINCE PAUL EHRLICH COINED THE PHRASE "magische Kugel," or "magic bullet," scientists have been striving to develop targeted therapies for diseases ranging from cancer to Crohn's disease. Although for many years the path toward this goal appeared to be pharmacologic in nature, four decades ago an important deviation was made: the advent of hybridoma technology. This allowed for the production of large quantities of antibodies specific for a single target: monoclonal antibodies. Now, the same molecules that were known to provide long-lasting protection against many infectious diseases had the potential to be harnessed for the treatment of many different diseases.

Although it took another decade for the first such therapy to be realized (muromonab, used to prevent transplant rejection), the floodgates have been opened. More than 30 monoclonal antibodies have been approved by the U.S. Food and Drug Administration, and many more candidates are in clinical trials. Antibody therapeutics are now a multibillion-dollar industry. Sliwkowski and Mellman (p. 1192) review several of the monoclonal antibodies now approved to treat cancer and their mechanisms of action. They also make the point that antibody therapies are not limited to monoclonal antibodies alone anymore; antibodies specific for more than one target (bispecific antibodies) and antibody-drug conjugates, among other strategies, are being pursued to generate therapeutics that are more specific, more stable, and more effective.

Monoclonal antibodies are also taking a front seat in the difficult task of developing vaccines against chronic infections such as HIV. Recent advances in the isolation of monoclonal antibodies from infected patients have allowed for the discovery of several very potent broadly neutralizing antibodies that target HIV. Klein *et al.* (p. 1199) discuss these antibodies and how they can inform HIV vaccine design and perhaps also be used therapeutically to treat infected individuals. A related News Focus (p. 1168) recounts how it took more than two decades for these broadly neutralizing antibodies to rise to the fore in HIV vaccine research, and how they have spawned provocative new strategies that have reinvigorated the field. How to generate protective antibodies through vaccination is a major hurdle, however, for treating HIV and many other infectious agents. Part of the reason for this is an incomplete understanding of the cells that make such protective antibodies, so-called memory B cells. Tarlinton and Good-Jacobson (p. 1205) discuss recent advances in this area, including the various types of memory B cells, how they are generated during an immune response, and how some of these processes could be shaped to our advantage during vaccination.

This special section highlights the great success of these "magic bullets," but it also shows that we have much to learn. The future of antibody-driven vaccine design and therapy is just now being glimpsed.

– KRISTEN L. MUELLER

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Antibodies

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REVIEW

Antibody Therapeutics in Cancer

Mark X. Sliwkowski and Ira Mellman

In a relatively short period of time, monoclonal antibodies have entered the mainstream of cancer therapy. Their first use was as antagonists of oncogenic receptor tyrosine kinases, but today monoclonal antibodies have emerged as long-sought vehicles for the targeted delivery of potent chemotherapeutic agents and as powerful tools to manipulate anticancer immune responses. With ever more promising results from the clinic, the future will likely see continued growth in the discovery and development of therapeutic antibodies and their derivatives.

Since the discovery in 1948 that cytotoxic folate antimetabolites could be used in the treatment of childhood leukemia, our basic approach to cancer therapy has remained fundamentally the same: surgery followed by sublethal administration of various cytotoxic compounds or radiation. However, over the past 16 years the situation has started to change substantially with the advent of "targeted" cancer therapies: the use of drugs developed to inhibit oncogenic proteins or survival factors selectively expressed by tumors. Although targeted agents are often thought of as low molecular weight inhibitors that can be given orally and gain access to cytoplasmic targets by diffusion across the plasma membrane, the first and perhaps most effective targeted therapies involve the use of biotherapeutics, recombinant proteins (usually antibodies) that modulate targets expressed at the cancer cell surface. This is quite remarkable because, not so long before the introduction of the first effective therapeutic antibodies in cancer (the CD20 antibody rituximab and the HER2 antagonist trastuzumab), there were severe doubts that antibodies could ever be safely used in humans. One major impediment was that monoclonal antibodies were typically produced in mice and therefore would be expected to be immunogenic in humans. The discovery that one could humanize murine antibodies by grafting complementarity-determining regions (CDRs) from the desired mouse antibody onto a recombinant human immunoglobulin backbone changed everything (*1*, *2*).

Today, a variety of sophisticated strategies exist to engineer humanized antibodies and to produce human antibodies by using rodents partially reconstituted with human immunoglobulin genes, human immune cells, or combinatorial phage or yeast display libraries that can yield high-affinity antibodies without requiring animal immunization at all (*3*). These approaches have led to an explosion of therapeutic antibodies both in cancer and in other diseases (*4*). Thus far, the only Food and Drug Administration (FDA)/European Medicines Agency–approved agents for oncology are conventional immunoglobulin G (IgG) molecules or their conjugates (Fig. 1), but engineered antibodies and novel antibody-like variants are increasingly making their way into clinical trials.

In this review we will discuss the general classes of antibody therapeutics that are commonly in use, provide a detailed analysis of two specific examples of oncogene-targeted antibody drugs, and consider some of the most promising new strategies, namely the use of antibodies for targeted delivery of conventional chemotherapeutics and to enlist the power of the immune system.

Classes of Antibody Therapeutics in Cancer

There are currently 13 antibodies approved by the FDA for various oncology indications (Table 1), and many more are currently being evaluated in clinical trials. Antibodies for the treatment of hematologic cancers, such as non-Hodgkin's lymphoma or chronic lymphocytic leukemia, and antibodies to B cell–associated targets (CD20, CD52) act, at least in part, because of their ability to induce apoptosis after binding to B cell tumors (*5*). The first of the approved antibodies directed against targets expressed on solid tumors were selected in cell culture as antagonists of the oncogenic receptor tyrosine kinases epidermal growth factor receptor (EGFR) and HER2 (*6*).

One antibody, bevacizumab, binds and sequesters vascular endothelial growth factor–A (VEGF-A), a key factor that is required for the growth of blood vessels and exerts its antitumor effect by functionally altering or slowing the formation of the tumor vasculature (*7*). Although this is at present the only approved antibody in oncology that targets a secreted protein, this class of therapeutic is common in the case of chronic inflammatory diseases, where multiple approved agents target proinflammatory cytokines such as tumor necrosis factor–α (*4*).

Two antibodies are now approved that are covalently modified with cytotoxic microtubule antagonists. These antibody-drug conjugates (ADCs), one of which is a modified version of trastuzumab for HER2-positive breast cancer patients (*8*), enable a form of targeted chemotherapy. These recent successes have led to a plethora of ADCs in clinical development (see below).

Last, the recent approval of ipilimumab has introduced yet another therapeutic strategy for anticancer antibodies, namely active immunotherapy (*9*). Ipilimumab blocks the activity of the negative regulator of T lymphocytes, CTLA4, resulting in the activation of a patient's immune response to cancer. This exciting approach has already demonstrated long-term, durable benefit.

Most of the approved antibodies in oncology are of the human IgG1 subclass, the subclass that is the most effective at engaging Fcγ receptors (FcγRs) on natural killer (NK) cells, macrophages, and neutrophils (Table 1). Antibody engagement of these receptors leads to the killing of antibody-bound target cells by antibody-dependent cellular cytotoxicity (ADCC) or antibody-dependent phagocytosis (ADP) (*10*–*12*). This is an important consideration given that ADCC or ADP likely contributes to the efficacy of these antibodies, above and beyond any direct effect on modulating signal transduction. FcγR-mediated cross-linking of surface-bound antibodies may be important in some settings, for example, to induce apoptosis (*13*).

The next generation of antibody therapeutics will likely extend beyond the IgG1 isotype and/or include modifications to the Fc domain, the region that binds to FcRs. Where it may be beneficial to reduce ADCC, the IgG4 subclass has been used, although here the hinge region of the antibody must be engineered to prevent premature dissociation and reassembly of heavy chain–light chain half molecules with endogenous IgG4s in the plasma (*14*). Complete elimination of ADCC can be achieved by modifying specific residues in the Fc domain that bind to FcγR or by producing recombinant antibodies that lack the N-glycosylation of heavy-chain Fc regions, required for recognition by FcγRs (*15*). Conversely, alterations in glycosylation have been identified that enhance FcγR binding (effector domain–enhanced antibodies), thereby increasing the potential for ADCC or FcγR cross-linking–dependent signaling. Still other Fc domain mutations are being tested that either enhance or reduce binding the neonatal FcR for IgG (FcRn), the receptor responsible for returning IgGs to the circulation after their internalization by endothelial cells. Thus, enhanced FcRn binding will serve to increase the half-life of injected antibodies, whereas reduced FcRn binding will decrease half-life (*16*). These may prove to be important considerations in controlling the pharmacokinetic exposure levels of a given antibody, with a potential toxicity possibly mitigated by faster clearance.

New formats are also being developed, such as two types of bispecific antibodies. In the first, single heavy chain–light chain pairs derived from antibodies with distinct specificities can be covalently or noncovalently linked to yield a single IgG molecule bearing arms targeted to two different antigens. To overcome the issue of monovalent binding that comes with this approach, phage

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display has been used to make single CDRs that exhibit dual specificities. Such dual-action Fabs are otherwise normal antibodies that retain high affinity and bivalent affinity for two antigens simultaneously. One such antibody (MEHD7945A) that detects EGFR and the HER3 co-receptor simultaneously is currently in phase II clinical trials (*17*). In other cases, one-armed antibodies (i.e., an intact IgG missing one Fab domain, onartuzumab) have been deployed where it was desirable to avoid the cross-linking of a potentially activating receptor (c-Met) (*18*).

Even less traditional formats are being evaluated, involving attenuated single-chain antibodies that have either single or dual specificities (*19*). These antibodies have the limitation that smaller antibody constructs have shorter in vivo half-lives after injection, which necessitates frequent or continuous injections. Larger, multiple-armed antibodies or antibodies genetically fused to other mediators (e.g., cytokines, hormones, and toxins) as well as a variety of synthetic "minibodies" and antibody mimetics are also on the horizon and, if successful, could increase the potential range of therapeutic strategies. However, one caution is that the farther one strays from the conventional, the greater the chances are for unanticipated behavior, adverse effects, or inherent immunogenicity.

EGFR Therapeutics

The EGFR family (ErbB/HER) has proved to be a fruitful area for the development of cancer therapeutics. To date, eight agents are approved for the treatment of various solid tumors, and at least a dozen other compounds are currently in clinical development.

EGFR therapeutics are divided into two classes, both of which inhibit EGFR: monoclonal antibodies (mAbs), cetuximab and panitumumab, and low molecular weight tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib. mAbs directed against EGFR were first developed in advanced colorectal cancer. The pivotal trial for cetuximab demonstrated tumor shrinkage when used in combination with the topoisomerase I inhibitor irinotecan in patients whose tumors were progressing on irinotecan-based therapy (*20*). Discernable single-agent cetuximab activity was also observed. The murine parent mAb, 225, was reengineered as a human chimera, which allows for ADCC. In contrast, panitumumab was derived from a transgenic mouse capable of producing human antibodies and exhibits considerably higher binding affinity for EGFR than cetuximab. Panitumumab is a human IgG2, which is less effective in mediating ADCC than IgG1 (*21*). Both antibodies are restricted to use in patients whose tumors overexpress EGFR and are wild type for the proto-oncogene KRAS but have not yet been compared directly, making it impossible to judge the contribution of ADCC.

Although both EGFR mAbs and small-molecule inhibitors have been commercially available for more than a decade, there is remarkably little overlap in how the two classes of antagonists are used clinically. Combining mAbs and small molecules is ineffective, despite preclinical data suggesting increased efficacy (*22*). Similarly, antagonism of EGFR was originally predicted to synergize with cytotoxic chemotherapy. Combination therapy of irinotecan with cetuximab was key to cetuximab FDA approval. Yet erlotinib or gefitinib failed to show clinical benefit in combination with several chemotherapies (*23*, *24*). Indeed, there is a suggestion that patient outcome may be worse when treated with the combination (*25*). Many factors contribute when preclinical observations fail to predict clinical responses, including differences in pharmacokinetics and, most importantly, differences in tolerability. Although both mAb and chemical inhibitors of EGFR cause skin rash, erlotinib and gefitinib cause additional toxicities that further limit tolerability when combined with conventional chemotherapies. Of interest in this regard is the recent clinical demonstration (and FDA approval) that erlotinib is more effective against tumors expressing an activated mutant allele of EGFR (*24*). Although both wild-type and mutant kinases are inhibited, selectivity for the mutant kinase might be expected to increase therapeutic index by sparing, relatively, the activity of the wild-type kinase in normal cells and tissues.

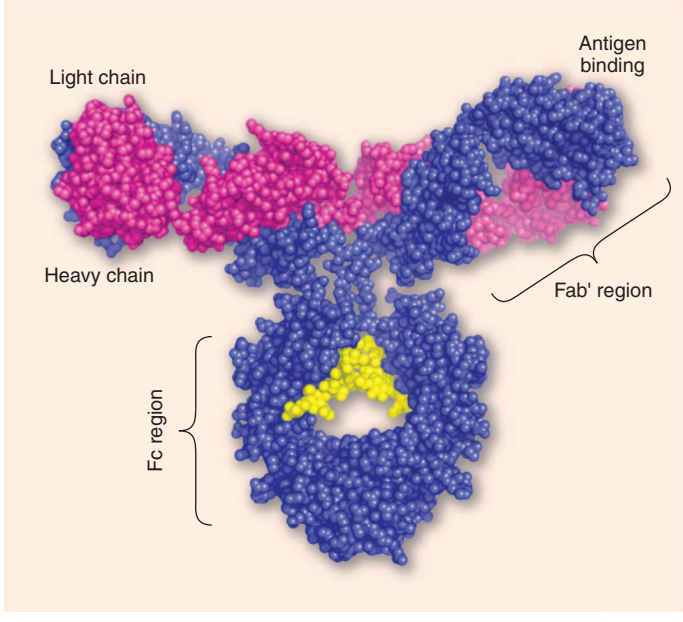


Fig. 1. Space-filling model of IgG1. Light chain, magenta; heavy chain, dark blue; carbohydrate, yellow. [Credit: C. Eigenbrot, Genentech, Incorporated]

HER2 Therapeutics

Three mAbs (trastuzumab, pertuzumab, and ado-trastuzumab emtansine) and a small-molecule TKI (lapatinib) are approved for the treatment of HER2-positive breast cancer (Table 1), yet interpretation of the clinical data is less complex than that observed with EGFR antagonists. Lapatinib, a low molecular weight HER2 and EGFR TKI, effectively blocks HER2 signaling and was approved on the basis of compelling clinical data generated in patients whose tumors had progressed on trastuzumab-based therapy (*26*). Thus, HER2 tyrosine kinase antagonism alone is an effective treatment for this form of breast cancer. Indeed, trastuzumab and pertuzumab, antibodies against HER2, were selected for their ability to block proliferation (*27*) and signaling activity (*28*). Although these antibodies were also humanized to IgG1, suggesting that ADCC might add to their clinical activity, human FcγR polymorphisms that enhance binding are not linked to improved responses in patients (*29*). Yet the relative importance of ADCC remains an active area of debate.

In contrast to EGFR antagonists, HER2-directed antibodies and small molecules are very effective in the treatment of HER2-positive breast cancer in combination with conventional chemotherapy. Because of favorable tolerability profiles, HER2 targeting can also be combined with standard cytotoxic chemotherapy. Indeed, pertuzumab is approved only in combination with trastuzumab and docetaxel (*30*). As is often the case in cancer therapy, the ability to combine multiple drugs produces better clinical outcomes; combinations are enabled by better safety profiles.

Because trastuzumab and pertuzumab bind to different regions of HER2 (Fig. 2), dual antibody therapy should allow for simultaneous antagonism of both activated forms of HER2. Support for this hypothesis was initially obtained in a phase II clinical trial that tested combination antibody therapy in patients whose tumors progressed on trastuzumab and cytotoxic chemotherapy. The findings in this trial demonstrated an objective response (tumor shrinkage) of 25% and a clinical benefit rate of 50% (*31*). A neoadjuvant (i.e., treatment before surgery) trial further confirmed that the antibody combination was also effective in patients who were naïve to therapy (*32*). Equipped with the knowledge that dual HER2 antibody blockade was active in early breast cancer and late-stage metastatic breast cancer, a pivotal trial validated the approach for the treatment of first-line metastatic breast cancer patients and led to the accelerated, full approval of pertuzumab in June 2012 (*30*). Indeed the magnitude of patient benefit, as measured

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Table 1. Antibody therapies and their indications.

Antibody type	Target	Tumor types	Dx test	Indication
Cetuximab (Erbitux; Bristol-Myers Squibb): chimeric human-murine IgG1	EGFR	Colon, head, and neck	Yes	Indicated for the treatment of *KRAS* wild-type, EGFR-expressing, metastatic colorectal cancer (mCRC) in combination with FOLFIRI [irinotecan, 5-fluorouracil (5-FU) leucovorin] for first-line treatment, in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy, as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan. In combination with radiation therapy for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck and in combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck. As a single agent, is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based therapy has failed.
Panitumumab (Vectibix; Amgen): human IgG1	EGFR	Colon	Yes	Indicated for the treatment of EGFR-expressing and *KRAS* wild-type mCRC with disease progression after fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens.
Trastuzumab (Herceptin; Genentech): humanized IgG1	HER2	Breast, gastric	Yes	Indicated for adjuvant treatment of HER2-overexpressing node-positive or node-negative breast cancer. As part of a treatment regimen containing doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel. Also with docetaxel and carboplatin. As a single agent after multimodality anthracycline-based therapy. For metastatic breast cancer in combination with paclitaxel for the first-line treatment of HER2-overexpressing metastatic breast cancer. As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease. In combination with cisplatin and capecitabine or 5-FU, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease.
Pertuzumab (Perjeta; Genentech): humanized IgG1	HER2	Breast	Yes	In combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.
Ado-trastuzumab emtansine (Kadcyla, Genentech): trastuzumab, derivative of DM1, 4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate linker	HER2	Breast	Yes	Treatment of patients with HER2-positive metastatic breast cancer who have received prior treatment with Herceptin and a taxane chemotherapy.
Bevacizumab (Avastin; Genentech/Roche): humanized IgG1	VEGF	Colon, non–small cell lung, glioblastoma, kidney	No	mCRC for first- or second-line treatment in combination with intravenous 5-FU–based chemotherapy. It is also approved to treat mCRC for second-line treatment when used with fluoropyrimidine-based (combined with irinotecan or oxaliplatin) chemotherapy after cancer progresses following a first-line treatment that includes Avastin. Advanced nonsquamous non–small cell lung cancer in combination with carboplatin and paclitaxel in people who have not received chemotherapy for their advanced disease. Metastatic kidney cancer when used with IFN-α. Glioblastoma when taken alone in adult patients whose cancer has progressed after prior treatment.

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Antibody type	Target	Tumor types	Dx test	Indication
Ipilimumab (Yervoy; Bristol-Myers Squibb): IgG1	CTLA4	Melanoma	Yes	Treatment of unresectable or metastatic melanoma in patients who have failed or do not tolerate other systemic therapy for advanced disease.
Rituximab (Rituxan/Mabthera; Roche): chimeric human-murine IgG1	CD20	NHL, chronic lymphocytic leukemia	No	As a single agent, in patients with relapsed or refractory, low-grade or follicular, CD20-positive, B cell non-Hodgkin's lymphoma (NHL). Previously untreated follicular, CD20-positive, B cell NHL in combination with first-line chemotherapy and in patients achieving a complete or partial response to Rituxan in combination with chemotherapy, as single-agent maintenance therapy. Nonprogressing (including stable disease), low-grade, CD20-positive, B cell NHL as a single agent after first-line CVP chemotherapy. Previously untreated diffuse large B cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens. Previously untreated and previously treated CD20-positive chronic lymphocytic leukemia in combination with fludarabine and cyclophosphamide.
Ofatumubab (Arzerra; Genmab): human IgG1	CD20	Chronic lymphocytic leukemia	No	As a single agent for the treatment of patients with chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab.
^{90}Y-labeled ibritumomab tiuxetan (Zevalin; IDEC Pharmaceuticals): murine IgG1, linker-chelator: tiuxetan (*N*-(2-Bis(carboxymethyl)amino)-3(Pisothio-cyanatophenyl)~propyl)-*N*-(2-Bis(car-boxymethyl)-amino)-2-(Methyl)ethyl)glycine	CD20	Low-grade or follicular B cell NHL	Yes	Treatment of B cell NHL (relapsed or refractory, low grade, follicular, transformed, or rituximab-refractory). Patients with previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy.
^{131}I-labeled tositumomab (Bexxar; GlaxoSmithKline): murine IgG2, direct covalent linkage to tositumomab	CD20	Low-grade or follicular B cell NHL	Yes	Treatment of patients with CD20-positive relapsed or refractory, low-grade, follicular or transformed NHL who progressed during or after rituximab therapy, including patients with rituximab-refractory NHL.
Alemtuzumab (Campath; Genzyme): humanized IgG1	CD52	Chronic lymphocytic leukemia	No	As a single agent for the treatment of B cell chronic lymphocytic leukemia
Brentuximab vedotin (Adcetris; Seattle Genetics): chimeric IgG1, MMAE, maleimidocaproyl valine-citrulline-PAB linker	CD30	Hodgkin's lymphoma	No	For the treatment of patients with Hodgkin lymphoma after failure or autologous stem cell transplant (ASCT) or after failure of at least two prior multiagent chemotherapy regimens in patients who are not ASCT candidates. The treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multiagent chemotherapy regimen
Gemtuzumab ozogamicin (Mylotarg; Wyeth): humanized IgG2), *N*-acetyl gamma-calichaemicin dimethyl hydrazide, AcBut hydrazone linker	CD33	Acute myelogenous leukemia	Yes	Withdrawn from the market in June 2010. Previously indicated for the treatment of patients with CD33-positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy.

by progression-free survival (3.9 versus 6.1 months) (*33*) and overall survival (*34*), is greater than what was observed for the initial approval of trastuzumab.

In summary, the advent of mAbs to oncogenic receptor tyrosine kinases of the EGFR family has represented a major advance in cancer therapy. Yet, there have also been attempts that have not yet led to success in the clinic, using mAbs to target other signaling receptors. Notable among these are antibodies to insulin-like growth factor 1 receptor, despite this receptor having a mechanistic link to many types of cancer. On the other hand, antibodies to c-Met continue in clinical development. The number of mAbs tested in clinical trials is small, which makes it difficult to draw any clear lessons yet. However, it should be noted that effective antibodies against solid tumors tend to recognize targets that are either subject to mutation (EGFR, c-Met) or overexpression (HER2) in cancer, even if the antibody itself is inactive against the mutant allele. Conceivably, mAb therapy against signaling receptors may prove most effective in cases where targets can be shown genetically to be important drivers of cancer or clear drivers of resistance to other forms of therapy.

Antibody-Drug Conjugates (ADCs)

The concept that antitumor antibodies could be used as vehicles for the selective delivery of cytotoxic agents to tumors has been around nearly as long as mAbs. However, until very recently, the idea has eluded successful implementation, probably for three reasons: (i) the use of antibodies against targets that were not sufficiently restricted to tumor cells, (ii) the use of drugs with insufficient potency or (in the case of bacterial or plant toxins) that were immunogenic, and (iii) the linker chemistry used to attach drugs to antibodies was not optimized. The latter consideration is

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one that required an enormous empirical effort to solve. A linker that was too labile allowed too much of the toxic drug to dissociate from the antibody in the blood. This then exposed normal tissues to the freed drug and, as a result, reduced the doses of the ADC that could be used. Stable linkers require complete proteolytic digestion of the ADC, releasing the derivatized amino acid, linker, and cytotoxic drug as the active metabolite (*35*). Similarly, the choice of drug required a great deal of trial and effort, with current successes being seen by using microtubule antagonists.

Gemtuzumab ozogamicin was the first ADC to reach the market in 2000. It is directed against CD33, a surface glycoprotein characteristic of acute myeloid leukemia (*36*). The conjugate is composed of a humanized IgG4, a pH labile linker, and calicheamicin, a very potent DNA minor groove binder. Unfortunately, the drug was withdrawn from the market in 2010 because of the failure of subsequent confirmatory studies to reproduce the initial clinical benefit profile (*37*, *38*).

More recently, brentuximab vedotin, a mAb against CD30 that was covalently modified with the microtubule antagonist monomethyl auristatin E (MMAE), was approved for use in advanced Hodgkin's lymphoma given its efficacy and good safety profile (*39*). The linker used to tether MMAE to the antibody contains a peptidic moiety that was designed as a substrate for cathepsin B; the antibody was delivered to cathepsin B–containing endosomes and lysosomes after internalization by the CD30-positive lymphoma cells (*40*).

Another ADC that has also recently gained approval is T-DM1, which is composed of trastuzumab (T) conjugated to a maytansine derivative (DM1) (*41*). In this instance, the linker is designed not to be cleaved by lysosomal proteases, suggesting that the drug is released only after limited digestion of the entire antibody. T-DM1 was found to prolong progression-free survival (9.6 versus 6.4 months) and overall survival (30.9 versus 25.1 months) in late-stage HER2-positive breast cancer patients who progressed on multiple other treatments (*42*).

The clinical successes of T-DM1 and brentuximab vedotin have stimulated a great deal of activity in developing ADCs to different solid and hematologic tumor targets using mAbs to a variety of antigens, most often conjugated to microtubule antagonists (MMAE and DM1 or their derivatives). In addition, new toxic payloads and linkers are under development in an effort to further increase therapeutic index and provide for combination therapy.

Novel engineered antibody platforms are also being investigated. For example, the typical cleavable MMAE linker drug (vc-MMAE) is coupled to antibodies after the reduction and then the derivatization of endogenous cysteine residues normally engaged in interchain disulfide bonds. Methods are being developed to engineer specific conjugation sites (e.g., unpaired cysteine residues) and defined sites on the heavy or light chains, leading to greater ease of conjugation and control over the number of drug molecules per antibody molecule (*43*). Other modifications are also being investigated in an effort to increase specificity of cancer cell binding (e.g., use of bispecific antibodies that recognize two antigens at once) or decrease the nonspecific uptake of the ADCs by normal cells that do not express the targets. Use of antibody-conjugated nanocarriers loaded with cytotoxic agents is also under investigation. Although this would increase the payload delivered after endocytosis, a potential limitation is the nonspecific loss of the cytotoxic in the plasma. We anticipate that the next several years will witness explosive growth and innovation in this area.

Antibodies and Cancer Immunotherapy

As was true for ADCs, the concept that a patient's immune system could be activated to generate anticancer responses has been actively explored for >30 years. For most of this time, however, little progress was made in the clinical arena, largely because of our incomplete knowledge concerning the functional organization of the immune system and how tumors manipulate the immune response. Moreover, much of the field was long fascinated by anticancer "vaccines," an approach limited by the immunosuppressive tumor microenvironments (*44*). Many cancer patients make anticancer T cell responses because tumors nearly always express mutant proteins or antigens to which the immune system is not tolerized and therefore are immunogenic. Yet these responses rarely manifest in clinical benefit.

An appreciation has now emerged that overcoming immunosuppression and enhancing the quality of the immune response may be key to developing effective cancer immunotherapies (*3*). This realization has generated enormous interest and excitement fueled by the early clinical successes of two classes of mAbs. The first of these is ipilimumab, which inhibits CTLA4, a negative regulator expressed on the surface of all T cells (Fig. 3A) (*45*). CTLA4 normally binds to CD80/CD86 on the surface of antigen-presenting cells, providing a powerful brake or checkpoint that limits the activation and proliferation of

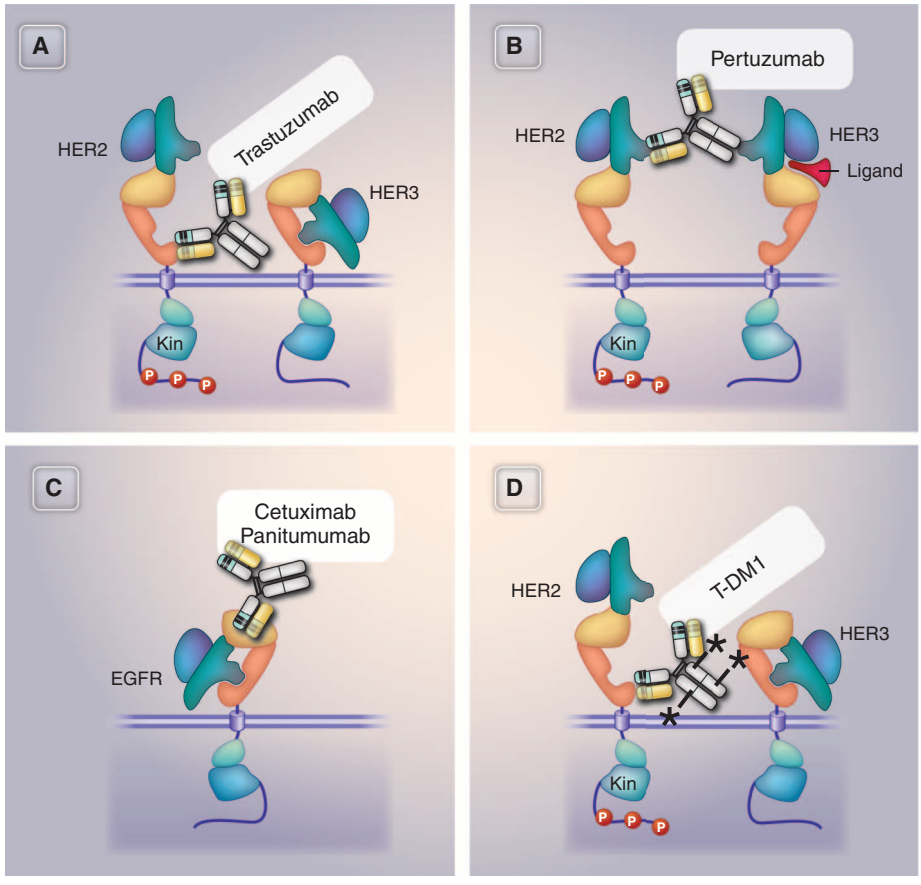


Fig. 2. Epitope binding of HER2 and EGFR therapeutic antibodies. (**A**) Trastuzumab. (**B**) Pertuzumab. (**C**) Cetuximab or panitumumab. (**D**) T-DM1 (ado-trastuzumab emtansine). In the case of HER2 signaling, a functional and physical association with a second related receptor, HER3, is often important (*60*). HER2 kinase phosphorylates the HER3 cytoplasmic domain, activating it as a scaffold to promote the phosphatidylinositol 3-phosphate kinase cascade. Conversely, activation of HER3 by binding ligands such as heregulin can allosterically activate HER2 kinase. Pertuzumab's likely mechanism of action is to block heterodimerization of HER2 and HER3. Asterisks indicate a cytotoxic agent, derivative of maytansine 1 (DM1).

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T cells after recognizing their cognate antigen. Ipilimumab blocks this interaction, thereby releasing the checkpoint and amplifying T cell responses. CTLA4 blockade also induces the death of regulatory T cells, which contribute to the immunosuppressive tumor microenvironment, by a mechanism that is still being characterized (possibly ADCC in the tumor bed; ipilimumab is an IgG1) (*46*, *47*). In the clinic, ipilimumab was found to provide robust and long-term survival benefit or cures to patients with late-stage metastatic melanoma who otherwise had no other treatment options (*9*). Although the percentage of patients receiving benefit was small (3-year survival of 23.5% versus ~10% in a control arm) and cannot yet be diagnostically defined, the results are impressive and led to ipilimumab being approved by the FDA in 2011. Subsequently, ipilimumab has been reported to exhibit varying levels of clinical activity in other indications, but its use is complicated by the fact that it also induces occasionally serious immune-related adverse events (e.g., autoimmune inflammation). In any event, these studies established critical proof of concept for checkpoint inhibitors specifically and for other immunomodulators in general.

Following closely behind the success of ipilimumab are mAbs that antagonize the interaction of programmed death–1 (PD-1), another negative regulator of T cells, with its ligands PD-L1 and PD-L2 (Fig. 3B) (*48*). Two antibodies against PD-1 (nivolumab and lambrolizumab) and one to PD-L1 (MPDL3280A) are the most advanced in the clinic. Although not as powerful of a brake as CTLA4, PD-1's role is to prevent the unrestrained activation of T cells that have been previously activated. PD-L1 is often expressed by tumor cells or immune cells infiltrating into tumors. Evolutionarily, its role probably developed as a regulatory node in viral immunity, preventing T cell hyperactivation and bystander killing of non-infected cells during virus infection: For example, normal cells react to interferon-γ (IFN-γ) release by local effector T cells by expressing PD-L1 to protect themselves against T cell killing. In cancer, tumor cells are thought to react in much the same way upon entry of tumor-specific IFN-γ–secreting cytotoxic T cells. Thus, the binding of tumor PD-L1 to PD-1 on activated T cells inhibits their effector function. Mechanistically, this appears to occur by the recruitment of a phosphatase to the PD-1 cytoplasmic domain that inactivates the phosphatidylinositol 3-kinase pathway in T cells, exhausting their ability to generate or release cytotoxic granules (*49*). Thus, the PD-1/PD-L1 axis serves as a front-line mechanism of immune suppression in the tumor bed. PD-L2 in particular is also expressed by dendritic cells and may play a role in maintaining peripheral tolerance.

Both preclinically and clinically, the addition of mAbs to either PD-1 or PD-L1 blocks their interaction, thereby rescuing T cell cytotoxic activity; often, this results in rapid and substantial tumor shrinkage coupled with long-term, durable responses (*48*). Presumably because the primary mode of action is to overcome immunosuppression of antitumor T cells in the tumor bed (as opposed to anti-CTLA4, which amplifies the production of T cells of all specificities in lymph nodes),

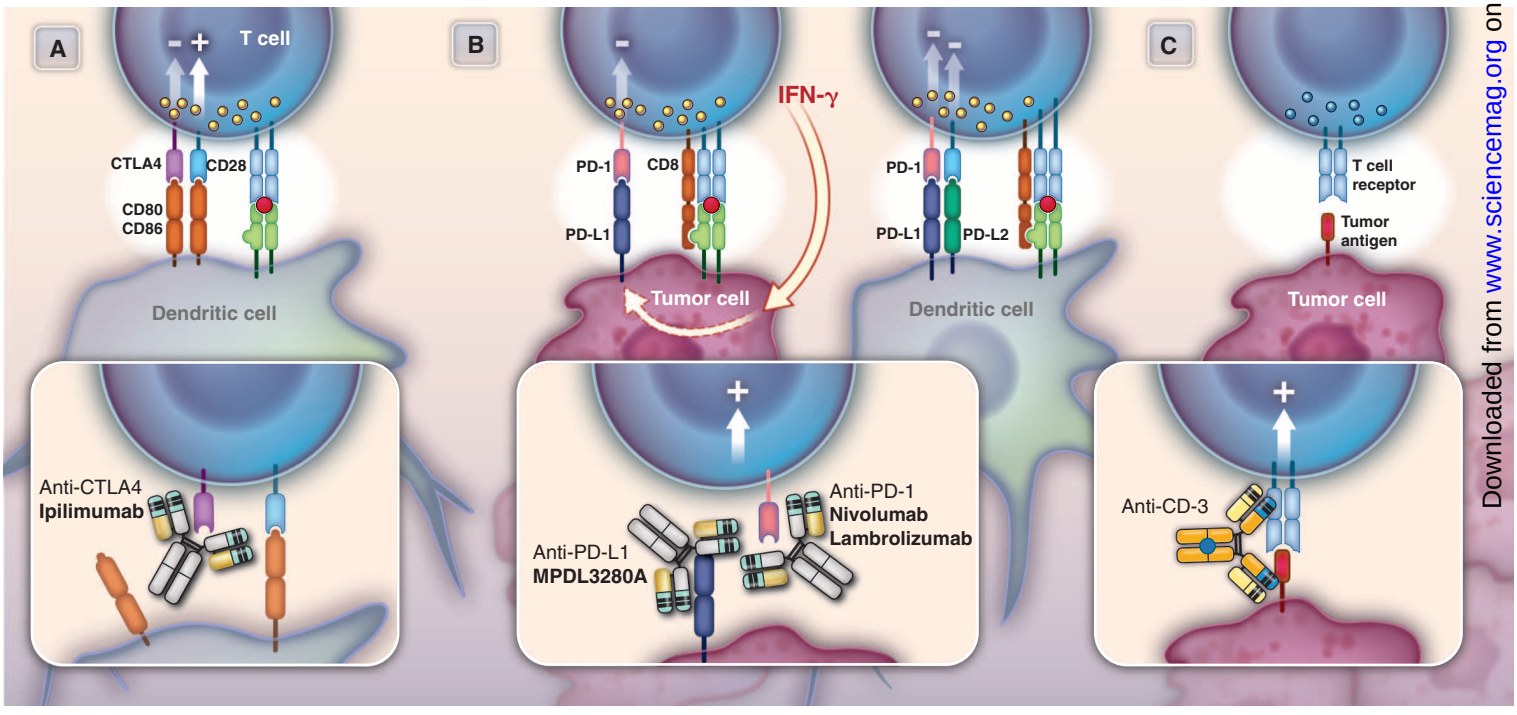


Fig. 3. The use of antibodies in active and passive immunotherapy of cancer. (**A**) Checkpoint blockade by anti-CTLA4. CD80 and CD86 are ligands expressed on the surface of activated dendritic cells during the presentation of MHC [human lymphocyte antigen (HLA)]–peptide complexes to T cell receptors. CD80/86 binds to the costimulatory molecule CD28 to help activate T cell proliferation and then to the checkpoint inhibitor CTLA4 to attenuate T cell proliferation. The antibody ipilimumab blocks the interaction of CTLA4 with its ligands, thereby releasing the checkpoint inhibitor and favoring T cell proliferation. (**B**) Checkpoint blockade and inhibiting immune suppression by anti-PD1 or anti–PD-L1. (Left) T cell influx into tumors results in the release of IFN-γ, which up-regulates PD-L1 expression by tumor cells. PD-L1 binds to PD-1, which is expressed by activated T cells, generating a negative signal that causes T cell exhaustion (inhibiting the ability of T cells to recognize and kill their targets). (Right) During antigen presentation by dendritic cells, PD1 can also act as a checkpoint inhibitor where a negative signal can be sent by its binding to either PD-L1 or the closely related (and dendritic cell–specific) negative regulatory ligand PD-L2. Generally, inhibition of both PD-L1 and PD-L2 (e.g., by anti–PD-1) is required to block negative regulation by dendritic cells, whereas only PD-L1 inhibition (by anti-PD-1 or anti–PD-L1) should relieve immunosuppression (immune rheostat) activity in the tumor bed. Note that, for clarity, only the primary interactions of PD-1, PD-L1, and PD-L2 are illustrated. (**C**) Bispecific antibodies against CD3 passively recruit cytotoxic T cells to tumor cells. Blinatumomab is a single-chain bispecific antibody that is composed of an anti-CD3 arm that recognizes the T cell receptor and an anti-CD19 arm that recognizes a surface antigen on the surface of B cell lymphoma cells; diagrammed is a conventional bispecific IgG for clarity. Recruitment of the T cells to the tumor cells in this way results in efficient tumor cell killing, as if the T cell had recognized its cognate peptide-MHC on the tumor cell target.

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adverse events associated with PD-1/PD-L1 blockade appear substantially less serious than with ipilimumab. Although registrational trials are just now getting under way, preliminary suggestions are that mAbs against both PD-1 and PD-L1 are active (*50*–*54*); it is too soon to know whether one or the other approach will distinguish itself on the basis of safety or efficacy. In this respect, it is interesting to note that PD-1 blockade will also inhibit interactions of T cells with PD-L2 on antigen-presenting cells (especially in the lung), which may or may not increase chances for toxicity; pneumonitis is a risk factor in patients treated with nivolumab, anantibody against PD-1. In addition, the PD-1 antibodies in the clinic are of the human IgG4 subclass with reduced potential for ADCC compared with the PD-L1 antibody, which has been engineered to completely eliminate FcγR binding and has yet to elicit serious pneumonitis (*53*). This difference or the difference in target (PD-1 versus PD-L1) may or may not correlate with increased efficacy or safety.

Given the complementary mechanisms of action of ipilimumab and the anti–PD-1/L1 antagonists, a recent clinical study has demonstrated that the two agents can show impressive additive activity, as well as additive toxicity, in melanoma (*55*). Because different criteria were used to judge clinical responses in this versus single-antibody trials [e.g., use of Response Evaluation Criteria in Solid Tumors (RECIST) versus World Health Organization (WHO) criteria for tumor shrinkage], further study will be required to understand the degree of enhanced benefit.

Antibodies that block immune checkpoints and immune suppression in the tumor bed have produced long-term, durable patient responses rarely seen with other therapeutics and, as such, may again change the face of cancer therapy similar to the initial antibodies against EGFR and HER2 15 years ago. It is likely that the coming years will see many more antibodies in this space as additional regulatory targets, both cell-associated and secreted, are identified and investigated.

Other Related Approaches

At some level, all therapies involving mAbs are immune therapies in that the immune system was required to produce and engage the therapeutic. However, it is useful to regard immunotherapies as ones that seek to actively manipulate the immune system, most often the T cell compartment, as is the case for antibodies to CTLA4, PD-1, and PD-L1. Hybrid approaches are already being introduced. One example of note is a specific single-chain antibody, blinatumomab, comprising tandem single-chain Fv fragments that bind CD19 on lymphoma and normal B cells and CD3, the antigen receptor of T cells (*56*). Treatment of patients with this small protein is effective at depleting non–Hodgkin's lymphoma cells by recruiting T cells to tumor cells and activating their cytotoxic effector function regardless of the T cell's own inherent specificity. Although active in early clinical trials, it is rapidly cleared from the circulation because of its small size, necessitating continuous infusion. Future work will no doubt investigate modifying the platform to enable more convenient dosing (Fig. 3C).

Another approach accomplishes the same task, except by fusing the anti-CD3 specificity to soluble, recombinant T cell receptors that can be selected to detect tumor-specific peptide–major histocompatibility complex (MHC) class I molecules (*57*). As above, T cells are recruited regardless of their inherent specificity and triggered to become antitumor effectors.

A third approach involves genetically modifying a patient's own T cells to express a membrane-bound antibody against tumors fused to signaling molecules that trigger T cell killing when the modified T cell detects a cognate tumor cell. The T cells (CARs) have yielded a promising result, at least in hematologic cancer in early clinical trials (*58*).

Last, conventional antibodies can be generated with engineered Fc domains that increase, rather than decrease, FcγR binding, in order to recruit macrophages and NK cells to mediate ADCC (*59*).

The Past, Present, and Future

Antibody therapeutics in cancer have a rich history, an exciting present, and a promising future. Although it is uncertain what new platforms will emerge as being efficacious and useful, it is certain that many new approaches will be tried in the years to come. The use of antibody therapeutics in combination with each other is also emerging. Indeed, compelling phase I data have recently been reported for dual immune checkpoint therapy using ipilimumab and nivolumab (*55*). These combinations have the potential to significantly lower or, in some cases, eliminate the amount of cytotoxic chemotherapy that is still currently the backbone of most oncology treatments. Systemic treatment of patients, which includes targeted mAb therapy, before surgery is also emerging (*32*). Moreover, one could imagine scenarios where these approaches are likely to reduce the need for extensive surgery. New delivery platforms, new approaches to ADCs, and new ideas to manipulate the immune response or the tumor microenvironment are certainly on the horizon and bode well for a renaissance of interest in antibody biochemistry and function, as well as for cancer patients.

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REVIEW

Antibodies in HIV-1 Vaccine Development and Therapy

Florian Klein,[1*] Hugo Mouquet,[2] Pia Dosenovic,[1] Johannes F. Scheid,[1] Louise Scharf,[3] Michel C. Nussenzweig[1,4*]

Despite 30 years of study, there is no HIV-1 vaccine and, until recently, there was little hope for a protective immunization. Renewed optimism in this area of research comes in part from the results of a recent vaccine trial and the use of single-cell antibody-cloning techniques that uncovered naturally arising, broad and potent HIV-1–neutralizing antibodies (bNAbs). These antibodies can protect against infection and suppress established HIV-1 infection in animal models. The finding that these antibodies develop in a fraction of infected individuals supports the idea that new approaches to vaccination might be developed by adapting the natural immune strategies or by structure-based immunogen design. Moreover, the success of passive immunotherapy in small-animal models suggests that bNAbs may become a valuable addition to the armamentarium of drugs that work against HIV-1.

Effective vaccines usually require potent antibody responses to block infection and/or clear the pathogen (*1*). For all vaccines that have been developed, the protective antibodies are directed to invariant molecular components of the pathogen. Even in the case of the influenza virus, in which the envelope spike is constantly evolving, the seasonal vaccine elicits antibodies that target parts of the spike that are shared by the dominant circulating viral species (*2*). In contrast, an effective HIV-1 vaccine would need to induce antibodies that target a large number of rapidly evolving contemporaneous viral strains in which the envelope spikes differ by as much as 35% in their amino acid sequence (*3*). Besides presenting the immune system with a diverse and moving target, HIV-1 displays only a small number of functional envelope spikes per virion with a high density of rapidly shifting glycans that shield sites of potential vulnerability (*4*–*9*). Thus, a vaccine to this pathogen would have to induce high-affinity antibodies that penetrate the glycan shield and bind effectively to sparsely expressed and highly diversified envelope spikes.

The possibility that such antibodies might exist was supported by clinical studies that revealed that 10 to 30% of individuals who had been infected for 2 to 4 years develop serologic activity with the ability to neutralize diverse viral isolates (*10*–*13*). Among these individuals, some (around 1%) exhibit exceptional cross-clade activity and potency and are referred to as elite neutralizers (*14*). Although serum from elite neutralizers has not been tested directly, the principle that antibodies in serum could be protective against HIV-1 was established by passive transfer of pooled human serum to chimpanzees, which were then protected from infection with HIV-1_{IIIb} (*15*). However, efforts to molecularly characterize the protective antibodies in human sera were stymied because of the limited nature of the techniques available for human antibody cloning.

First-Generation bNAbs

Despite technical limitations, several groups were able to identify antibodies against HIV-1 with broad neutralizing activity (bNAbs). Although not very potent, this initial group of antibodies defined some of the sites of HIV-1 vulnerability on the envelope spike, which consists of three gp120-gp41 heterodimers (Fig. 1). These sites included the third hypervariable domain (V3) loop of gp120 [e.g., the 447-52D antibody (*16*)], the binding site for CD4, which is the primary receptor for viral entry [b12 (*17*)]; the CD4-induced site that is the viral binding site for the co-receptor [e.g., 17b (*18*)]; viral glycans [e.g., 2G12 (*19*)]; and the membrane proximal external region (MPER) of gp41 [4E10 and 2F5 (*20*, *21*)]. In vitro, the most broad and potent antibodies in this initial group were b12 [geometric mean of the median inhibitory concentration (IC_{50}) from selected strains 3.1 μg/ml, breadth 40%]; 2G12 (3.0 μg/ml, 27%); 2F5 (3.6 μg/ml, 58%); and 4E10 (2.7 μg/ml, 96%) (*22*). Moreover, besides in vitro neutralization, passive transfer of b12, 2G12, 2F5, or 4E10 protected against SHIV [simian immunodeficiency viruses (SIVs) that express the HIV-1 envelope glycoprotein] infection in macaques (*23*–*29*).

Despite these achievements, there was little enthusiasm for the possibility of an antibody-based vaccine, because all of the initially characterized antibodies were unusual. 2G12 has three combining sites, instead of the usual two (*19*, *30*); 2F5 and 4E10 are self-reactive (*31*, *32*); and finally, b12 is a phage-derived antibody generated by random pairing of heavy and light chains that may have never existed in nature (*17*). Consistent with their unusual features, innumerable attempts to elicit these antibodies by vaccination were not successful. Most important, however, the amount of these antibodies required for complete protection in macaques was thought to be too high to be achieved by vaccination (*33*). Consistent with these ideas, all envelope-based HIV-1 vaccines failed and, as a result, much of the vaccine effort focused exclusively on T cell–mediated immunity that also has failed to prevent HIV-1 infection to date.

A New Beginning

Two very recent developments have refocused attention on antibody-based HIV-1 vaccines. First, single-cell antibody cloning techniques were developed and introduced as a means to systematically study and obtain HIV-1 envelope-reactive antibodies (*34*–*37*). Second, modest levels of reduced risk of infection in the RV144 human vaccine trial were correlated with antibody responses to the HIV-1 envelope spike (*38*, *39*).

Efficient methods for human antibody cloning from single cells were initially developed to study mechanisms that govern tolerance in the B cell compartment (*37*). These methods were adapted in order to identify single B cells that express antibodies that bind to the HIV-1 envelope spike (*34*, *35*, *40*) or cultured B cells that were screened for the production of neutralizing activity (*41*, *42*). When applied to individuals with high serum titers of HIV-1 neutralizing activity, these methods uncovered a large number of new antibodies that were up to 2 to 3 orders of magnitude more potent than those that were previously discovered (*41*–*45*). Protection experiments with one of the new antibodies in macaques showed that serum concentrations of as little as 15 μg/ml were completely protective against high-dose challenges of $SHIV_{SF162P3}$ (*46*), and similar results were also obtained in mice (*47*, *48*), which together suggest that sterilizing antibody responses might, in fact, be possible to achieve by vaccination.

The RV144 trial refocused attention on antibodies because modified intention-to-treat analysis revealed a 31% ($P = 0.04$) reduction in infection that correlated with the presence of antibodies that bind to the V1/V2 region of the envelope spike (*38*, *39*). It is noteworthy that the antibody response induced by the vaccine does not neutralize primary HIV-1 isolates, and it has been proposed that the effects were mediated instead by antibody-dependent cellular cytotoxicity (ADCC) (*49*). However, this idea has not been proven directly. Although nonneutralizing antibodies showed effects in some studies (*50*), they failed to effectively protect against infection in mice (*47*) and, in other studies, in nonhuman primates (*51*). Therefore,

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the precise mechanism of protection in the RV144 trial is unknown.

Second-Generation bNAbs and Their Target Sites

What is the molecular basis for broad and potent serologic neutralizing activity in HIV-1–infected individuals that develop these responses? Single-cell antibody cloning experiments revealed that some humans produce a neutralizing response to HIV-1 by targeting two or more different sites on the envelope spike (*34*, *40*, *44*, *52*, *53*), whereas in others, serum neutralizing activity could be accounted for by one prominent antibody clone (*41*–*44*).

To date, the new bNAbs have been found to target four major "sites of vulnerability" on the HIV-1 envelope spike (Fig. 1) (*54*). These include the CD4-binding site (CD4bs), the N160 glycan-dependent site associated with the V1/V2 loops, the N332 glycan-dependent site at the base of the V3 loop, and the MPER on gp41 (Fig. 1). Additional sites of vulnerability are likely to be discovered, as exemplified by 8ANC195 and 3BC176, that recognize yet-to-be-defined epitopes that are distinct from the four major target sites (*22*, *40*, *44*).

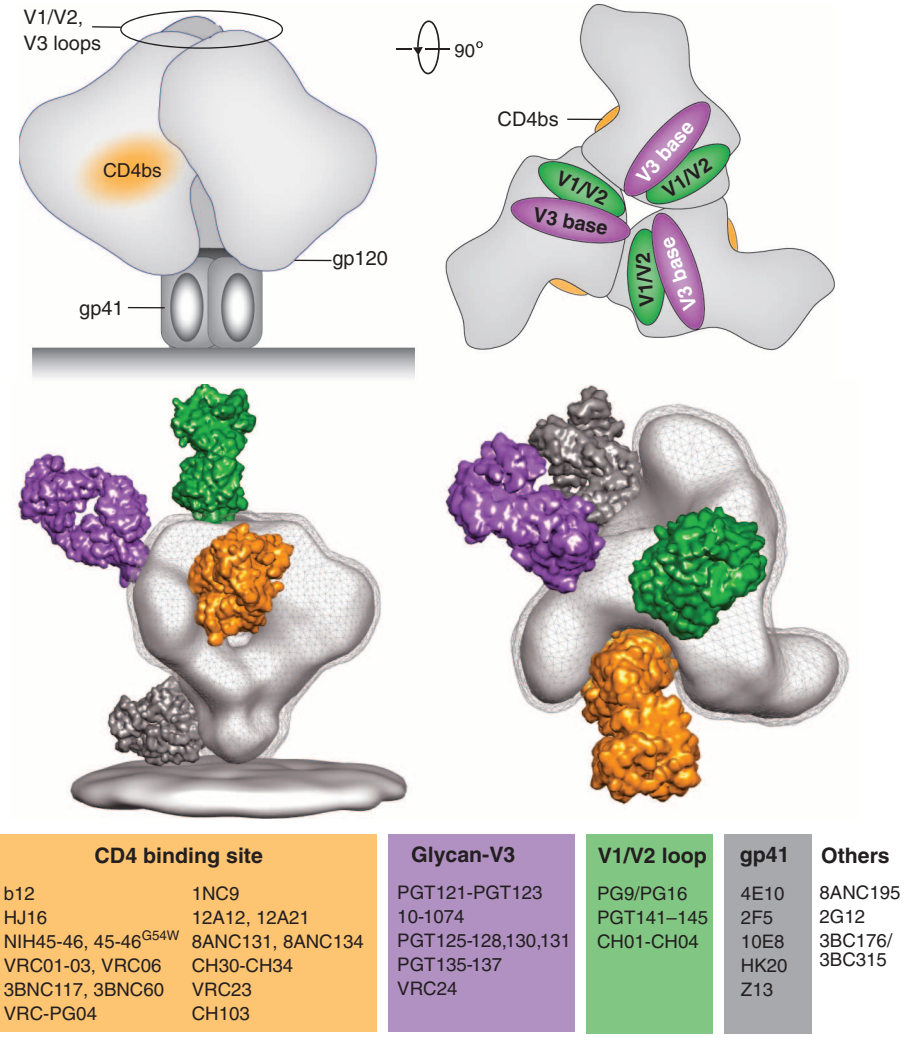
The CD4bs is a protected site in that it is recessed and surrounded by glycans and variable regions (*55*). Nevertheless, this functionally conserved site is accessible to CD4 and the CD4bs antibodies. The most potent of the new bNAbs targeting the CD4bs (e.g., NIH45-46 and 3BNC117) are derived from the same germline variable heavy chain (V_H)-gene segment V_H1-2 (*44*, *56*–*58*). Structural analysis revealed that, although they were isolated from different individuals, V_H1-2 antibodies share a common mode of antigen recognition whereby framework residues contribute to CD4 mimicry (*44*, *56*–*58*). A short complementarity-determining region 3 of the light chain (CDRL3) interacts with the gp120 V5 and diversity (D) loops, and a short CDRL1 circumvents clashes with glycans at Asn^{276} on the D loop (*44*, *56*–*58*).

The N160 glycan–V1/V2 site is targeted by the antibodies PG9 and PG16, CH01 to CH04, and PGT141 to 145 (Fig. 1) (*41*, *42*, *52*). Structural analyses showed that these antibodies penetrate the glycan shield with a long anionic CDRH3 (third complementarity determining region of heavy chain variable regions) that contacts a β-strand on gp120 and interacts with N-linked glycans from two adjacent gp120 protomers in the trimeric envelope complex (*59*, *60*). Moreover, binding of PG9 to the envelope spike seems to alter the stability of the trimer (*60*) and might contribute to its potent neutralizing activity.

The N332 glycan–V3 loop site is targeted by PGT121- and PGT128-like bNAbs (Fig. 1) (*42*, *45*, *61*). A crystal structure of PGT128 bound to its ligand shows that it contacts the C-terminal end of the V3 loop, mannose $Man_{8/9}$ glycans, and a synthetic Man_5 glycan lacking the core *N*-acetylglucosamine ($Man_5GlcNAc_2$) at positions N332 and N301, respectively (*61*). PGT121-like antibodies also contact gp120 at the base of the V3 loop, and a high mannose- or a complex-type *N*-glycan at N332 (*45*, *62*). Although the two classes of antibodies likely approach the N332 site from different angles, both seem to block infection by interfering with CD4 binding (*62*).

10E8 targets the MPER in gp41 (Fig. 1). This antibody recognizes an α helix, and unlike 2F5 and 4E10, which were less-potent first-generation antibodies targeting a closely related site, 10E8 is reported not to be auto- or phospholipid-reactive (*63*).

Vaccine design efforts have focused on independent targeting of the four major sites of vulnerability on the envelope spike, but it is still unclear how frequently each of these sites are targeted by antibodies that develop during natural infection. For example, the most recent estimates based on serologic studies and computational methods indicate that only a fraction of the infected individuals that produce broadly neutralizing antibodies do so by producing a dominant CD4bs-specific monoclonal antibody with exceptional breadth and potency (*53*, *64*). However, only a few individuals have been studied comprehensively, and additional sites of vulnerability could still be discovered. It may, therefore, still be too early to make firm conclusions about the relative frequency with which antibodies to specific viral targets or their combinations contribute to the development of anti–HIV-1 serologic breadth and potency in infected individuals. Although the pro-



CD4 binding site		Glycan-V3	V1/V2 loop	gp41	Others
b12	1NC9	PGT121-PGT123	PG9/PG16	4E10	8ANC195
HJ16	12A12, 12A21	10-1074	PGT141–145	2F5	2G12
NIH45-46, 45-46^{G54W}	8ANC131, 8ANC134	PGT125-128,130,131	CH01-CH04	10E8	3BC176/ 3BC315
VRC01-03, VRC06	CH30-CH34	PGT135-137		HK20	
3BNC117, 3BNC60	VRC23	VRC24		Z13	
VRC-PG04	CH103				

Fig. 1. Antibody target sites on the HIV-1 envelope spike. Schematic representation of the HIV-1 envelope spike. Each of the monomer units of the trimer is composed of a gp120 and gp41 transmembrane protein. The four best-characterized broadly neutralizing target sites are highlighted and include the CD4-binding site (orange), the glycan-associated epitopes on the base of the V3 loop (purple), the V1/V2 loop (green), and the MPER on gp41 (gray). Electron micrograph–derived illustration of the envelope spike targeted by representative broadly neutralizing F(ab)s shown approximately to scale (bottom: NIH45-46, orange; PG16, green; PGT128, purple; 2F5, gray). Examples of first- and second-generation bNAbs that target these and other sites are color-coded and indicated at the bottom.

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cess of obtaining this information is costly, it may be particularly valuable in informing vaccine approaches, because neutralizing antibodies that develop naturally with greater frequency may also be easier to elicit by vaccination.

Characteristics of bNAbs

One of the surprising findings that emerged during the initial molecular characterization of the human HIV-1 antibody response is that envelope-directed antibodies are highly somatically mutated (*34*). Human immunoglobulin G (IgG) antibodies typically carry 10 to 20 V_H gene somatic nucleotide mutations (*65*). In contrast, HIV-1–specific IgG antibodies with limited neutralizing activity carry nearly twice as many mutations (*34*, *66*), whereas the heavy chain genes of the new generation of broad and potent neutralizers frequently carry more than 80 V_H mutations (*44*, *67*–*69*).

Somatic mutations are introduced into antibody genes during the immune responses to antigen in a defined microanatomical compartment, called the germinal center, that is located within secondary lymphoid organs (Fig. 2) (*70*). After interaction with cognate antigen and T cells, B cells enter the germinal center where they undergo clonal expansion, somatic mutation, and selection for B cells expressing high-affinity antibody variants (*70*). Mutation is focused on the CDRs of the antibody that typically contact the antigen. This maximizes the probability of altering the binding properties of the antibody and minimizes changes in the framework regions (FWRs) that form the conserved structural support for the antigen binding site (*71*–*73*). B cells that develop high-affinity antibodies are favored in the germinal center, because they capture greater amounts of antigen, which is then processed and presented to cognate T follicular helper cells that deliver a positive selection signal (*70*). The selection mechanism is subject to an affinity ceiling. Affinity is directly related to the "on" and "off" rates of the antibody: The higher the on rate, and the slower the off rate, the higher the affinity. Affinity selection is limited because the on rate is limited by diffusion, and the off rate is limited by the rate of antigen internalization (*74*, *75*). Once the antigen is inside the cell and being degraded, there is no added value to a slower off rate. Thus, any B cell with an antibody that has an off rate that is slower than the rate of antigen internalization is equally selected. Once the affinity ceiling is reached, there is no further value to additional somatic mutation, and B cells exit the germinal center as plasma cells or memory B cells (*70*). In humans, this affinity ceiling is usually reached by 10 to 15 nucleotide mutations in the V_H. Thus, the high levels of mutation in HIV-1 antibodies are unlikely to be the product of a single round of affinity maturation in the germinal center, and high levels of mutation imply multiple rounds of selection in response to a continually evolving pathogen (Fig. 2).

bNAbs are highly mutated and can also carry insertions and deletions, which are uncommon in other antibodies (*42*, *44*, *45*, *67*–*69*). When reverted to their germline sequences, the new bNAbs lose their neutralizing activity and even fail to bind to most HIV-1 envelope proteins, which raises the question of how B cells bearing these antibodies were stimulated to join the germinal center reaction to begin with (*44*, *56*, *76*, *77*). One possibility is that the germline antibody–expressing B cell was initially stimulated by a non–HIV-1 antigen and developed reactivity to HIV-1 by chance mutation (*78*). Another possibility would be that only some HIV-1 envelope spikes are able to activate B cells expressing the appropriate germline antibodies. This idea is supported by the finding that some SHIVs induce bNAbs, whereas others do not (*79*), and by a prospective study on an HIV-1–infected individual who developed a broad and potent CD4bs-specific antibody (see below) (*80*).

The exceptionally high number of somatic mutations in bNAbs was analyzed by investigating the role of mutations in the antibodies' FWRs. Unlike other antibodies, including HIV-1–reactive antibodies with limited neutralizing activity, bNAbs were found to require FWR mutations for their potent activity (*81*). In contrast to most other antibodies, mutations in the FWRs of bNAbs can contribute to neutralization breadth and potency by altering the antibody's flexibility and by enhancing direct contact with the antigen (*81*). This is of particular importance, because IgV genes have evolved to be more resistant against somatic mutations that alter the coding sequence of the FWR. Moreover, these mutations are normally selected against because they tend to destabilize the antibody scaffold that is required to support the CDRs. Therefore, the requirement for FWR mutation may in part explain why large numbers of mutations are required to generate most bNAbs.

A second unusual feature shared by some, but not all, of the new bNAbs is a long CDRH3, which can be used to penetrate the HIV-1 envelope glycan shield (*59*). For example, PG9 or PG16 and PGT145, which recognize a combination of carbohydrates and

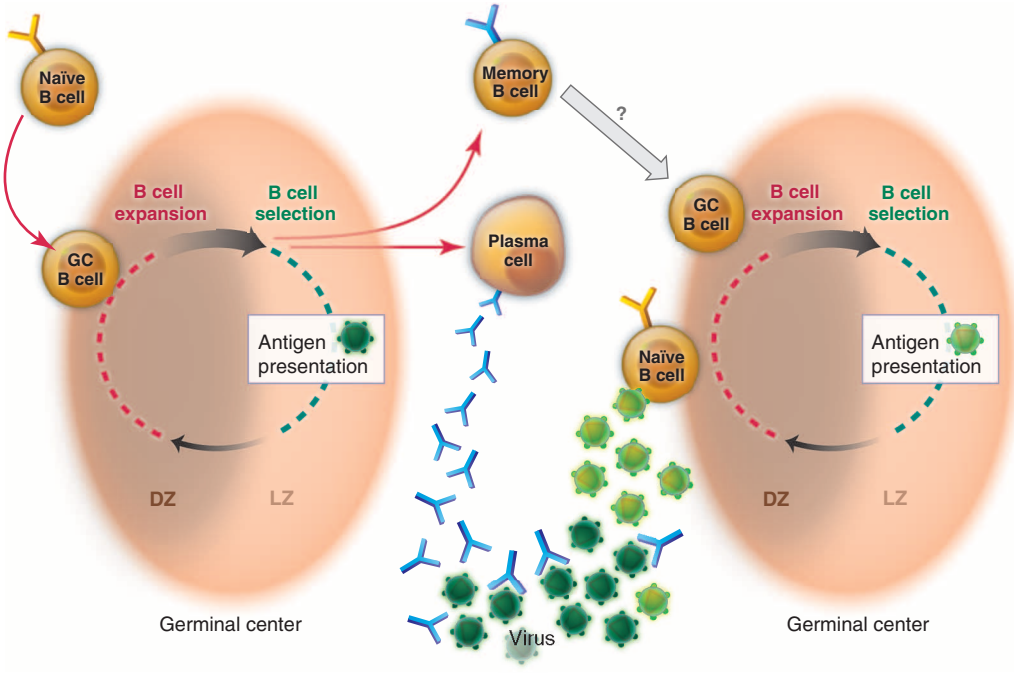


Fig. 2. Potential scenario of the HIV-1 envelope–specific B cell response. Naïve B cells selected by antigen interact with cognate T cells and are recruited to the germinal center. In the dark zone (DZ), B cells proliferate and express activation-induced deaminase, which results in the acquisition of somatic mutations. The cells of this expanded and diversified B cell clone migrate to the light zone (LZ), where they encounter the antigen (e.g., viral envelope protein, dark green) presented as immune complexes on the surface of follicular dendritic cells. High-affinity antigen-binding B cells that capture and present antigen to T cells are selected to return to the dark zone to proliferate or differentiate into memory B or plasma cells. High-affinity envelope-directed antibodies produced by the plasma cells exert selection pressure on the virus population, but viral escape variants emerge and expand (light green). Envelope antigens expressed by the selected virus clone are presented to either naïve B cells or memory B cells that have already encountered an HIV-1 envelope antigen, which reinitiates the cycle of clonal selection and somatic mutation.

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the V1/V2 loop, show exceptionally long CDRH3s. Moreover, long CDRH3s are found in antibodies that recognize a complex epitope composed of carbohydrates and protein at the base of the V3 loop, as well as in some of the antibodies to the CD4-binding site, and in 10E8 that targets the MPER (*82*).

Finally, antibodies cloned from HIV-1–specific memory B cells are frequently polyreactive (*66*, *76*). Polyreactivity refers to an antibody's ability to bind to a variety of different antigens with low affinity (*83*). Although polyreactivity is a normal feature of the human antibody system, it is selected against during B cell development (*37*). Polyreactivity increases, however, in the germinal center as a result of somatic mutation and selection, such that 23% of all memory B cells normally produce these antibodies (*65*). Memory B cells producing antibodies specific for the HIV-1 envelope spike are unusual in that ~70% are polyreactive (*66*, *76*). This property can be positively selected at two different steps in the development of HIV-1–specific B cells. Mature B cells expressing polyreactive anti–HIV-1 receptors are preferentially recruited into the germinal center reaction, and this property is often retained despite somatic mutation and affinity maturation (*76*). In addition, nonpolyreactive HIV-1–reactive B cells that enter germinal centers and undergo somatic mutation can also be selected for polyreactivity (*78*, *80*).

Why HIV-1 antibodies are selected for polyreactivity is unknown, but one potential explanation is that this property can increase the valency, and therefore the avidity, of these antibodies. It has been estimated that HIV-1 displays only ~15 functional envelope spikes per virion (*8*), and therefore, an antibody would have to bind monovalently unless it can bind to two separate monomers on the same trimer (*6*–*8*). In theory, polyreactivity would allow heterotypic binding by combining the recognition of the envelope spike with one Fab arm and a nearby polyreactive, or specific low-affinity, ligand with the other (*45*, *76*, *84*). This general strategy, which can be referred to as heteroligation, may be used by antibodies such as 2F5 and 4E10, which combine binding of gp41 and the viral membrane (*85*, *86*), and antibody 21c, which binds to both gp120 and CD4 (*84*).

Despite the prevalence of polyreactivity among all HIV-1 envelope–directed antibodies, most of the new bNAbs are not highly poly- or self-reactive. Exceptions include the less-potent first-generation bNAbs 2F5 and 4E10 that target the gp41 MPER (*31*, *87*); a few antibodies to the CD4bs (i.e., NIH45-46 and CH103, CH104, and CH106); and antibodies to the glycan-associated V1/V2 loops (i.e., CH01 to CH04) (*44*, *80*, *88*).

In conclusion, a low level of polyreactivity is a normal feature of the antibody system that appears to be used by HIV-1 antibodies to increase their affinity and/or avidity. It should not necessarily be viewed as an obstacle to the development of an HIV-1 vaccine.

New Approaches to HIV-1 Vaccination

Although passive transfer experiments in macaques and mice (*46*, *48*) strongly suggest that a vaccine that induces potent bNAbs would be protective against HIV-1, these antibodies have never been induced by immunization in humans (*89*). Characterization of the human antibody response to HIV-1 is starting to reveal some of the reasons why this has been so difficult and is providing some initial clues to rational approaches to this problem.

Given the unusual structural properties of bNAbs, it appears likely that HIV-1 vaccination will require alternatives to the traditional vaccine approaches. One possibility is to try to reproduce the natural sequence of events that led to the development of a potent bNAb by using HIV-1 envelope proteins obtained from infected individuals that developed such antibodies (*5*, *44*, *67*, *80*, *90*). This approach necessitates understanding of the coevolution of the virus and the antibodies in individuals that develop breadth and potency. Only one such study has been published to date (*80*). The authors of this study used single-cell antibody cloning techniques (*34*, *37*) to isolate the antibody CH103, the corresponding transmitted founder virus, and multiple intermediates from an African donor who developed serologic HIV-1 neutralizing activity (*80*). Sequence analysis revealed extensive epitope evolution by the virus and somatic mutation in the antibody preceding the development of breadth and potency (55% of HIV-1 strains were neutralized with a mean IC_{50} of 4.54 μg/ml). Most important, although the germline precursor of CH103 did not bind heterologous envelope proteins, it bound to the transmitted founder virus (*80*). Therefore, it seems unlikely that other envelope proteins would initiate the response that led to the development of the CH103 antibody. Mimicking envelope evolution by sequential immunization is therefore one approach to activate and then shepherd B cells expressing the correct germline antibody to evolve into bNAbs (Fig. 3).

A second nonmutually exclusive approach is to design the immunogen to specifically activate B cells expressing the germline precursors of bNAbs (*91*, *92*). For example, combinations of computational and genetic selection methods have been used to design antigens that can activate tissue culture B cells expressing the V_H1-2 germline precursors of the most potent CD4bs-specific antibodies (*91*, *92*). Used alone, these designer antigens may not induce bNAbs, but they could be potent stimulators of clonal expansion of the cells that can develop such antibodies, which might be a first step in a more complex immunization scheme (*91*, *92*).

An important impediment to developing an HIV-1 vaccine has been the use of large-animal models that necessitate low throughput and are not amenable to genetic experimentation. Systematic testing of new ideas and new HIV-1 vaccination approaches will necessitate the development of small-animal models that can allow rapid iterative experimentation and a mechanistic understanding of the immune responses required to induce protection by an HIV-1 vaccine.

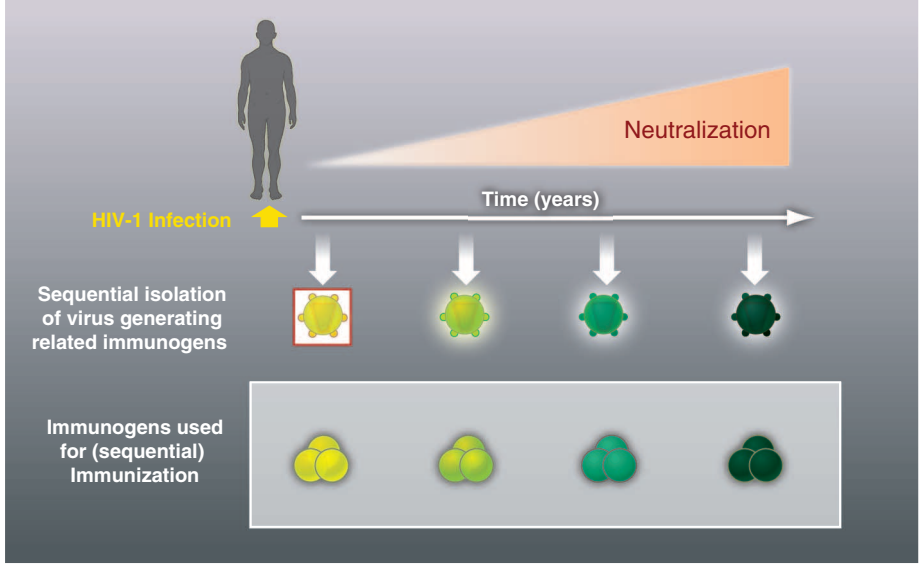


Fig. 3. Implications for vaccine design by studying HIV-1 and antibody coevolution in an individual with bNAbs. Longitudinal analysis of an HIV-1–infected individual was performed from the time of infection up to the development of bNAbs (*80*). The evolution of the HIV-1 envelope on the virus drives the diversification of the antibody response. Isolation and sequence analysis of the HIV-1 envelope on the founder virus (red square) and on viruses at later stages (light green to dark green) provides crucial information for generating antigens that can potentially elicit a broadly neutralizing antibody response. Mimicking the evolution of antigens in an HIV-1 vaccine approach is a promising strategy to elicit bNAbs in humans.

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HIV-1 Immunotherapy

Kitasato and von Behring first used serum antibodies as therapeutics for treating tetanus and diphtheria infection over a century ago. Today, serum therapy is still in use for snake and spider bites, as well as rabies postexposure prophylaxis. Furthermore, there are more than 30 U.S. Food and Drug Administration (FDA)–approved monoclonal antibodies for cancer, autoimmune, and infectious diseases (*93*). Despite these successes, it was generally believed that antibodies would have no role in HIV-1 therapy because of the rapid viral escape and the failure of the initial attempts at combination antibody therapy in humanized mice (*94*) and in humans (*95*, *96*).

In an early study, humanized mice infected with HIV-$1_{JR\text{-}CSF}$ or HIV-1_{SF162} were treated with a cocktail of the antibodies b12, 2G12, and 2F5. Although there was a transient decline in the viral load, viremia returned to baseline within 5 to 12 days, and therefore, it was concluded that even cocktails of bNAbs could not effectively control viremia (*94*).

Infected humans were also treated with an overlapping cocktail of three antibodies, namely, 2G12, 2F5, and 4E10 (*95*, *96*). Eight chronically and six acutely HIV-1–infected individuals on antiretroviral therapy (ART) with undetectable viral loads were selected for infection with viruses that were sensitive to at least two of the three components of the antibody cocktail in in vitro assays. ART was stopped one day after starting a course of 11 weeks of treatment with the antibody combination. Antibody therapy failed entirely in six out of the eight chronically infected subjects, and only two showed prolonged suppression of viremia (*95*). The results with the acutely infected subjects were more difficult to interpret because they had not been subjected to control treatment-interruption experiments. However, a single individual remained controlled with antibody alone for the entire treatment period and beyond. Of note, the only antibody that produced viral escape variants was 2G12, which suggests that only 2G12 exerted selective pressure on the virus (*95*). Very similar results were observed in an independent study with the same cocktail of antibodies given weekly for 12 weeks after ART interruption (*96*). Of the 10 acutely or early infected individuals enrolled in this study, 2 remained controlled throughout the treatment period, and again, the viruses that emerged during therapy were only resistant to 2G12 (*96*). Together, the two human studies suggest that, if there was an effect of immunotherapy, it was probably due to a single antibody with relatively low levels of activity compared with the recently discovered more potent bNAbs .

The overall conclusion of both the original mouse and human studies was that antibodies were not able to effectively control HIV-1 infection, because the virus rapidly escapes by selection of resistant variants (*94*–*96*).

The availability of the more-potent new-generation bNAbs prompted a reevaluation of immunotherapy in HIV-1–infected humanized mice (*97*). The mice used in these studies were immunodeficient and reconstituted with human hematopoietic stem cells (*98*, *99*). They were infected with HIV-1_{YU2}, a CCR5-tropic virus that is difficult to neutralize. Mice remained infected for more than 100 days, showed a decrease in the CD4/CD8 T cell ratio, as well as virus diversification. However, these mice do not produce strong T or B cell immune responses to the antigen, and they have impaired immune effector responses (*97*, *100*). The antibodies initially tested were 45-46^{G54W}, a CD4–binding site antibody (*57*); 10-1074 and PGT128, two N332 glycan-dependent antibodies (*42*, *45*); PG16, a N160 glycan-dependent antibody (*41*); and 3BC176, which targets a yet-to-be-defined conformational epitope (*40*). Although each of the antibodies was highly active against HIV-1_{YU2} in vitro, therapy with any single antibody caused only a transient decrease in viremia followed by a rapid emergence of escape variants (*97*). However, escape from the antibodies was restricted to a limited set of mutations in the antibody target sites, which suggested that combinations of antibodies directed to different sites on the envelope spike might be difficult to overcome (*97*). Indeed, long-term control of viremia was achieved when as few as three antibodies were combined (*97*, *101*). Moreover, because of the long half-life of the antibodies, viremia remained suppressed for an average of 60 days after cessation of treatment, which corresponded to the length of time that the antibody levels remained therapeutic (*97*). Finally, a few of the animals remained aviremic within the time of follow-up even after antibody concentration fell below therapeutic levels. Thus, combination HIV-1 immunotherapy differs from combination ART, because the longer half-life of the antibodies maintains viremic control for a long period of time after antibody administration is stopped. In addition, antibodies interfere with different aspects of the viral life cycle. ART prevents new infection by interfering with reverse transcription, integration, proteolytic processing, and/or viral entry. The precise mechanism by which antibodies suppress infection is unknown but may involve antibody-mediated increase in the rate of viral decay (*102*); killing of infected cells by ADCC (*103*); blocking infection by interference with CD4 binding (*44*, *56*, *57*); and blocking cell-to-cell and cell-free virus transmission (*104*). Whether the two modes of therapy might be complementary or even synergistic remains to be determined.

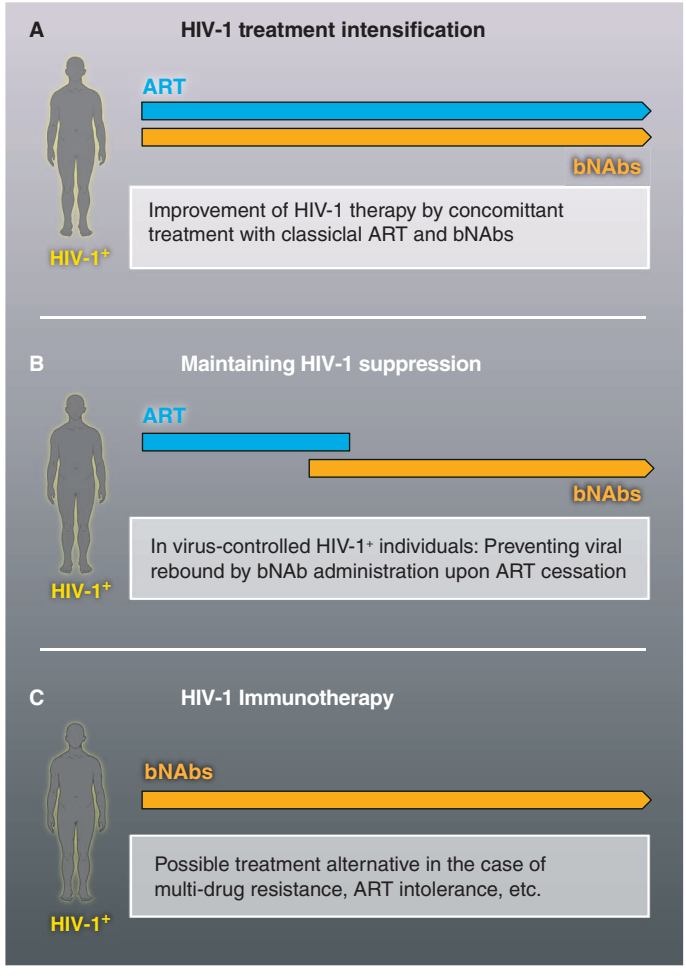


Fig. 4. Potential use of bNAbs in HIV-1 therapy. Suggested settings for the evaluation of bNAbs in clinical trials. (**A**) Different modes of action in ART and HIV-1–neutralizing antibodies might result in considerable HIV-1 treatment intensification in humans. (**B**) Prevention of viral rebound while ART is halted might be accomplished by HIV-1 antibody therapy. In order to reduce the likelihood of viral escapes from bNAbs, HIV-1–infected individuals should have fully suppressed viral loads before antibody therapy is started. (**C**) Treatment with a combination of bNAbs could be of particular interest, especially if individuals either do not tolerate ART (e.g., drug-drug interaction or severe side effects) or are resistant to it.

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Antibodies

The HIV-1 immunotherapy experiments in humanized mice established the concept that antibodies can be effective in suppressing HIV-1 infection, but they also raised a number of important questions that remain to be resolved. For example, can a vaccine that induces potent bNAbs be used therapeutically in individuals controlled by ART? Can antibody-based therapy be used instead of ART to provide long-term HIV-1 control without daily medication? Can vectors such as adeno-associated virus that have been used to direct antibody synthesis by the host and prevent infection (*48*, *105*) also be used to produce a long-term single-shot HIV-1 therapy? Can immunotherapy with antibodies be used as part of eradication strategies? Will immunotherapy interfere with HIV-1 transmission?

To evaluate the promising results obtained in experiments with humanized mice, we will first have to determine whether they can be reproduced in nonhuman primates. SHIV-infected macaques support a far higher overall viral burden and diversity than mice, and the disease resembles HIV-1 in that it is a chronic infection that can lead to immunodeficiency. Moreover, macaques have an adaptive immune system and an intact effector cell compartment, whereas humanized mice do not. These immune system components cannot eliminate the virus but they do contribute to regulating the viral load and are essential to maintaining the level of set-point viremia. We speculate that adaptive and innate components of the immune system will facilitate viremic control by antibody therapy in intact hosts. Should the mouse immunotherapy experiments be confirmed in macaques, iterative experimentation in mice and macaques will expedite the development of new immunotherapeutic approaches.

Experiments in macaques should precede human studies, but they may not be entirely predictive because SHIV infection in macaques differs from HIV-1 infection in humans in a number of important ways. Whether and how antibodies can be used to control infection in humans can only be resolved in clinical trials (Fig. 4).

In conclusion, over the past 4 years, the landscape for HIV-1 immunotherapy and vaccine development has changed dramatically as a result of antibody-cloning efforts. The next years should reveal whether these results can be effectively translated into the clinic.

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REVIEW

Diversity Among Memory B Cells: Origin, Consequences, and Utility

David Tarlinton[1,2]* and Kim Good-Jacobson[1,2]

Immunological memory is the residuum of a successful immune response that in the B cell lineage comprises long-lived plasma cells and long-lived memory B cells. It is apparent that distinct classes of memory B cells exist, distinguishable by, among other things, immunoglobulin isotype, location, and passage through the germinal center. Some of this variation is due to the nature of the antigen, and some appears to be inherent to the process of forming memory. Here, we consider the heterogeneity in development and phenotype of memory B cells and whether particular functions are partitioned into distinct subsets. We consider also how understanding the details of generating memory may provide opportunities to develop better, functionally targeted vaccines.

Successful vaccination rests on immune memory. Exposure to a pathogen or its products typically elicits an immune response that kills, clears, or neutralizes the invader. Despite such functional success, immune responses may continue in two crucial ways (*1*). First, antibody production may persist for months or years, providing protection while the amounts of antibody remain sufficiently high. Second, pathogen-specific lymphocytes persist in a resting state, circulating through the body but able to be reactivated rapidly to produce more antibody if re-exposure to the same pathogen overwhelms existing amounts. When a memory response is activated, the antibodies made differ from primary responses in several ways (*2*). The class or isotype of the secreted antibody is usually switched and is no longer immunoglobulin M (IgM), which dominates the early stages of the primary response; antibody appears in the serum more promptly than on first exposure; the affinity of the antibody for antigen (Ag) is higher than in the beginning of the primary response, sometimes by orders of magnitude. Thus immune memory resides both in the antibody that continues to be made and in the B cells and T cells that can rapidly combine to make more antibodies, reproducing previous, successful immune responses.

The formation of an isotype-switched, high-affinity memory B cell population is usually associated with T cell–dependent (TD) antibody responses, meaning those requiring T lymphocyte involvement (Fig. 1). TD responses are characterized by the rapid development of antibody-secreting cells (ASCs), Ig isotype switching, and the appearance of histological structures called germinal centers (GCs). GCs are sites where the processes mediating affinity maturation of the B cell receptor (BCR) for antigen occur and from which class-switched memory B cells and long-lived plasma cells (LLPCs) arise (*1*, *2*). A GC-centric view of B cell memory, however, does not explain the complexity known to exist in memory. For example, there is B cell memory to T cell–independent (TI) antigens that do not generate functional GCs (*3*). Also, for TD Ag, there are memory B cells that have not switched isotype, that do not have variable (V) gene somatic hypermutation (SHM), and/or that have arisen independently of GCs (*4*). Furthermore, it appears that for a given Ag, the breadth of BCR specificities against that Ag differ between the memory B cell and LLPC populations—broader in memory than in plasma cells (*5*). It is emerging also that different functions are segregated between different classes of memory B cells, with properties such as longevity and rapidity of reactivation being enriched in distinct compartments. If these instances become generalities, then understanding the criteria by which B cell memory compartments are populated during a response may substantially alter the way in which antigens are configured or delivered to maximize protective vaccination.

Classical Germinal Center–Dependent B Cell Memory

B cell differentiation in response to TD antigens is considered classically to develop along two pathways; one leads rapidly to the appearance of clusters of ASCs, and the second leads to the appearance of GCs and memory (Fig. 1). The basis for the bifurcation of B cell differentiation along these pathways remains poorly understood. Although high-affinity BCR for antigen and early expansion of ASCs has been noted (*6*), it may be amplifying by proliferation the choice already made, rather than influencing differentiation (*7*). The context of the antigen, however, may be a more fundamental regulator of this differentiation, with some immunization strategies generating ASC foci at the expense of GCs. For example, a targeting system delivering antigen to marginal zone–associated dendritic cells generated extrafollicular ASCs without GCs or memory unless Toll-like receptor (TLR) 7 or 9 agonists were included (*8*). Although this reflects the ability of TLR agonists to promote GC development (*9*), it shows also that the context of the antigen is crucial in early differentiation (*10*).

The foci of ASCs, located outside the B cell follicles (i.e., extrafollicular) of the secondary lymphoid organs (SLO), initially secrete IgM and, later, isotype-switched antibodies (*11*–*13*). There is little evidence of V gene SHM or improved binding affinities for antigen among these cells (*14*, *15*) and, typically, these ASCs undergo apoptosis in situ within days of being formed (*13*, *16*). Thus, these early ASCs provide an immediate, germline-encoded antibody response to an immune challenge that can be crucial to combating the pathogen (*16*) but contribute little, if anything, to B cell memory.

GCs also appear within days of challenge (*12*), are located within B cell follicles of SLOs, and can persist for weeks or months depending on the Ag (*17*–*20*). They are composed predominantly of B cells with minor, crucial populations of follicular dendritic cells (FDCs) and specialized CD4 helper T cells called follicular helper (T_{FH}) cells. FDCs, nonhematopoietic cells derived from perivascular precursor cells (*21*), are specialized in retaining antigen on their surface by binding immune complexes via receptors specific for complement or immunoglobulin Fc regions and may also provide survival signals to GC B cells. T_{FH} cells arise by a distinct developmental pathway dependent both on the transcription factor Bcl6 and interaction with antigen-specific and bystander B cells (*22*–*24*). T_{FH} cells are specifically equipped to sustain and modulate the GC reaction, expressing molecules that mediate B cell proliferation, differentiation, and—by maintaining expression of the enzyme activation–induced cytidine deaminase (AID)—V region gene diversification by SHM (*22*, *23*). The development and properties of T_{FH} cells are not a major focus of this review and have been excellently assessed elsewhere.

GCs are the sole documented sites for coupling the diversification of BCR V gene sequences by SHM, with the selective expansion of those variants with improved binding affinity for antigen as a result of that SHM (*2*, *25*). The iterations of V gene mutation and B cell selection that increase the average affinity of the GC B cell population over time is referred to as affinity maturation (*2*). The preferential expansion of high-affinity B cell clones in the GCs appears to be mediated by competition for T_{FH} cells and the molecules they express and secrete. Higher-affinity BCR is thought to translate into improved antigen acquisition by GC B cell variants, and

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thus greater possibility of meaningful conjugation with T_{FH} cells in the GCs that, in turn, may provide the proliferative and differentiation signals that enable the dominance of clones with improved affinity (*25*), because it is apparent that survival alone is insufficient to drive affinity maturation in the GCs (*26*, *27*). Affinity-matured memory B cells and LLPCs, formed by what might be quite distinct triggers, emigrate from the GCs under the direction of T_{FH} cells. That is, the memory B cell compartment appears to be less stringently selected for affinity compared with the LLPC compartment (*28*), which may reflect different mechanisms by which these differentiation events are initiated. As descendants of the one B cell clone can form foci of ASCs and GCs (*29*), it has been proposed that passage through the GCs confers on B cells the properties of memory, such as longevity and recall sensitivity (*30*, *31*). So, if one uses SHM and affinity maturation as key characteristics of B cell memory, the GC is the origin of memory B cells and long-lived plasma cells (*2*). It is now clear, however, that there are more ways to memory than via the GC.

GC-Independent B Cell Memory

The formal demonstration that memory B cells could be generated independently of GCs in response to TD antigens is one of the more im-

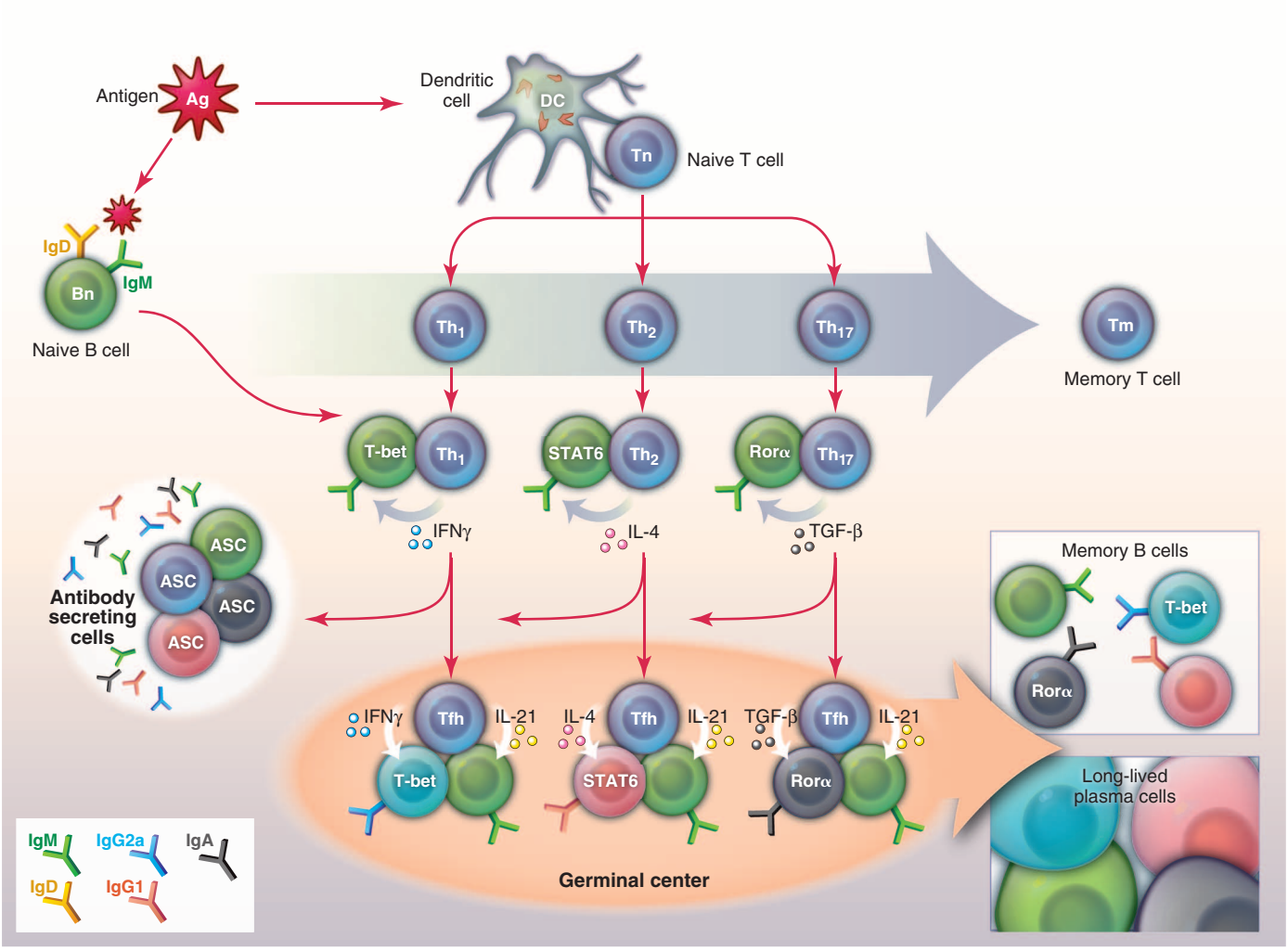


Fig. 1. Characteristics of a primary antibody response. During a humoral TD response, naïve B cells (Bn), expressing IgM and IgD, and naïve T cells (Tn) are activated by Ag, either directly or after processing by a dendritic cell (DC). Activated T cells, dictated by their priming, are polarized to one of several T helper (T_H) cell types, each associated with a distinct cytokine profile. Independently of the interaction with B cells, T cell activation leads to T cell memory (Tm). We depict here the classical view of T_H1 (secreting IFN-γ, regulated by T-bet), T_H2 (secreting IL-4, regulated by GATA3), and T_H17 (secreting TGF-β, regulated by Rorα) cells. B cells, induced to proliferate by T cell–derived signals, undergo immunoglobulin class-switch recombination (CSR), differentiation into ASCs, or a combination of both (class-switched ASCs). CSR in B cells is dictated by T_H-derived cytokines and the transcription factors they induce. Shown here are IFN-γ–inducing T-bet in B cells, required for CSR to IgG2a in mouse; IL-4 inducing STAT6, usually required for CSR to IgG1 and IgE; and TGF-β inducing Rorα, required for CSR to IgA. Activated B and T_H cells may also up-regulate the transcription factor Bcl-6 and establish GCs in which, through V gene mutation and B cell selection, the affinity of the antibody for antigen is improved. T_H cells in the GCs, called T_{FH} cells, are distinct from early T_H subsets, secreting IL-21 in addition to other, priming-specific cytokines. From the GCs, affinity-matured LLPCs and memory B cells are produced, expressing immunoglobulin isotypes that reflect the T_H type in the initial priming. It now appears that the persistence of switched memory B cells depends on continued expression of the transcription factors required for their induction—T-bet for IgG2a and Rorα for IgA. Thus, the appearance of different classes of antibody, specialized in clearing specific types of pathogens, in the memory compartments can be traced back to the initial interactions between DC and T cells. A complication of a deterministic system is in responses inducing multiple cytokines, such as in influenza, and whether these operate independently, competitively (overlapping graded expression of transcription factors within cells), or are localized to specific tissues.

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portant recent shifts in the understanding of B cell memory (*32*). Mice whose B cells lack the transcriptional repressor Bcl6 do not make GCs, nor do they generate antigen-specific LLPCs in the bone marrow (*32*–*34*). Yet, these B cells generate class-switched memory B cells that completely lack V gene SHM and thus affinity maturation (*32*). Bcl6-deficient memory B cells are indistinguishable from their Bcl6-expressing counterparts by cell surface phenotype, turnover, recall behavior, and, excepting mutated V genes, gene expression profiles, suggesting that passage through the GC is not essential to confer the properties of memory (*35*). As noted earlier, Bcl6 is also intrinsically required for the development of T_{FH} cells, which are also required for GCs. T_{FH} cell formation, however, is not required for the appearance of GC-independent (GCi) memory B cells (*35*).

Where in an immune response to a TD antigen might one expect GCi memory B cells to arise? As noted (*35*), the early stages of the B cell response, before GC formation, appear to be the points at which GCi memory arises. For a productive immune response, activated B cells must interact with activated CD4 T cells that are specific for the same antigen (*36*). This interaction is achieved by having activated B cells and T cells reposition themselves along the interface of the B and T cell areas within SLO through alterations in the expression of key chemokine receptors: CCR7 on the B cells and CXCR5 on the T cells (*36*, *37*). The lengthy interactions between cognate T and B cells results in the movement of B cells to the outer- or interfollicular regions (*38*, *39*) (Fig. 2). Activated T cells, which are not yet T_{FH} cells, accompany the B cells and continue to interact, resulting in B cell proliferation (*38*–*40*) and a potential point of developmental bifurcation. Some of the proliferating B cells up-regulate Bcl6 (*39*), which by gene repression allows the B cells to move to the FDCs in the follicles, where, in concert with their cognate T cells that are now T_{FH} cells, GCs form (Fig. 2). Of the B cells remaining in the outer follicle, some migrate out and establish the foci of ASCs (*36*), whereas others may be the B cells that are the origin of GCi memory (Fig. 2). This scheme is consistent with the appearance of GCi memory in the absence of Bcl6 and the onset of Bcl6 expression.

Although it is difficult to prove, given the extensive similarity between GCi and GC-derived memory B cells (*35*), circumstantial evidence points to GCi memory as a component of normal immune responses. First, recirculating, isotype-switched, antigen-specific B cells early in a TD response have memory characteristics but an absence of SHM in their V genes, implying a pre-GC origin (*41*). Second, an activated pre-GC B cell population gave rise to memory B cells before GC cells after adoptive transfer (*42*). Third, unmutated V gene sequences are relatively frequent among isotype-switched memory B cells of unmanipulated mice (*43*). Fourth, blocking GC formation by treatment shortly after immunization with antibodies that inhibit essential T cell–B cell interactions such as those between CD40L and CD40 and ICOS (inducible T cell costimulator) and its ligand ICOSL, resulted in isotype-switched, phenotypically normal memory B cells that had no evidence of SHM or affinity maturation (*35*, *44*). Curiously, the Ag targeting strategy that produced exclusively extrafollicular ASCs did not generate GCi memory (*8*), suggesting that GCs and GCi memory develop after the split of the ASC pathway.

Collectively, it appears that GCi memory is generated early in the immune response after the interaction of Bcl6-negative, antigen-specific B and T cells (Fig. 2). Given this timing, it may be that the BCR specificities present in this population reflect the initial responding B cell population before antigen-driven selection. Examination of this memory population in a polyclonal response with a broad range of starting BCRs and with the possibility of multiple isotypes being generated will help clarify this point, revealing the range of binding and whether there is an association with isotype. Thus, GCi memory may provide a means of retaining a broad range of antigen-specific B cells, not molded by affinity maturation to particular determinants on the immunizing antigen and thereby providing protection against related but distinct antigens (Fig. 3). Whether an equivalent population exists among human memory B cells is unclear (*45*–*47*).

The Importance of Class

Heterogeneity of memory B cells is not limited to GCs or GCi but extends to functional differences associated with the class of immunoglobulin the cells express. That is, specialized functions such as differentiation into plasmablasts and self-renewal may segregate into different memory B cell populations. If this is the case, then knowledge of the types and ratios of memory B cells produced by

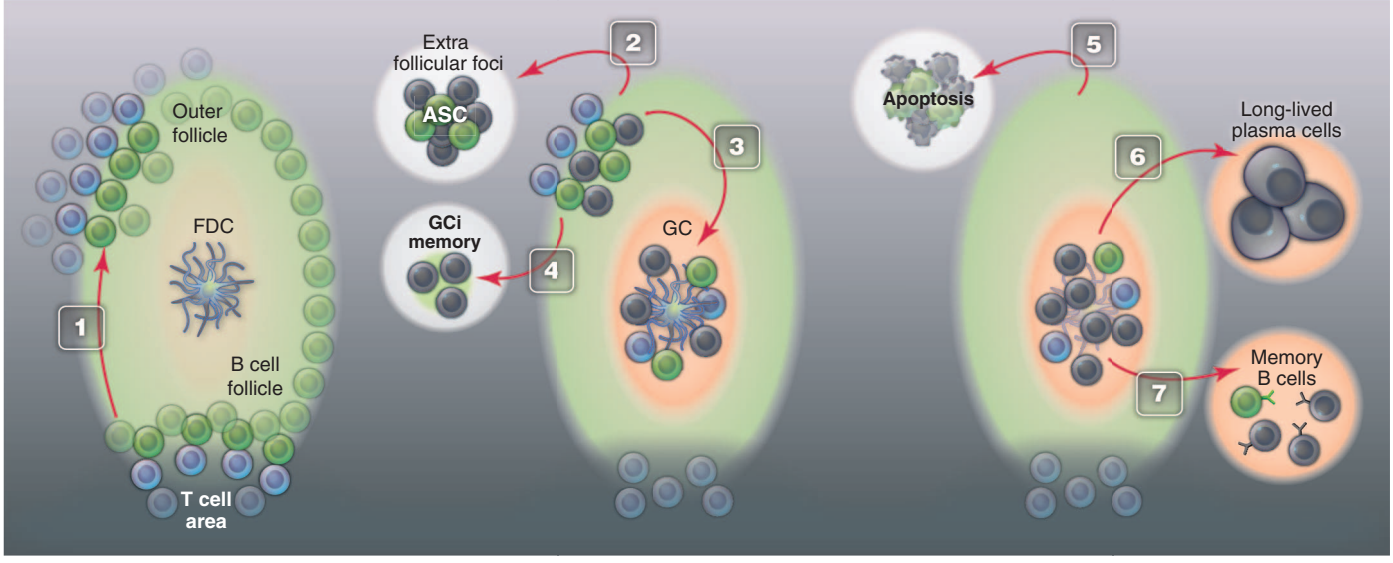


Fig. 2. Pathways to memory. Antigen-activated B cells and T cells align on the borders of the B cell follicles and the T cell areas of secondary lymphoid organs, establishing stable interactions and allowing B cells to receive T cell signals. (**1**) Activated B and T cells then migrate to the outer follicle, where B cells undergo proliferation and cytokine-directed CSR (black cells). From among these B cell blasts, some migrate and differentiate into ASCs, giving rise to the extrafollicular foci (**2**). Others return to the follicle, localizing on FDCs, to form GCs, which requires the help of T_{FH} cells (**3**). As the immune response progresses, ASCs in the foci undergo apoptosis (**5**), while the GCs give rise to conventional, affinity-matured and isotype-switched long-lived plasma cells (**6**) and memory B cells (**7**). We propose that GCi memory arises from the outer follicle (**4**), comprising both CSR and IgM cells and reflecting the repertoire of the initial activated B cells.

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different infections or adjuvants/vaccines may reveal mechanisms underlying the different half-lives of humoral immunity that different types of responses produce.

The humoral system has evolved to respond to different types of pathogens by inducing particular immunoglobulin classes that are the most efficient at clearing those infections, such as IgG2a for antiviral responses (*48*). Two recent papers link the ability of memory B cells to persist or to differentiate rapidly into plasmablasts during recall responses to isotype (*49*, *50*). In both studies, activation of isotype-switched memory B cells resulted in plasmablast differentiation only; the cells did not reenter GCs. In contrast, IgM memory B cells established GCs, albeit poorly, which correlated with the presence of antigen-specific antibodies; IgM memory B cells that were isolated and transferred into naïve recipient mice underwent robust isotype switching and GC formation. Furthermore, IgM memory B cells survived in mice for at least 450 days at near-peak frequency, whereas IgG memory B cells declined from their peak value at an approximately exponential rate. Both compartments contained mutated sequences, although the frequency of mutated sequences and mutations per V gene were fewer in IgM than in IgG memory B cells (*49*). Thus, IgM memory arises—possibly not exclusively—from the GCs and does so early [numbers peaked at ~d10 (*49*)], as has been proposed for human IgM^+ memory B cells (*45*, *51*).

Although the mechanisms underlying the functional differences between IgM and switched memory B cells are unknown, molecules that regulate the formation of different switched memory subsets are being discovered. During immune responses, antigen-activated B cells integrate multiple environmental cues that dictate cellular

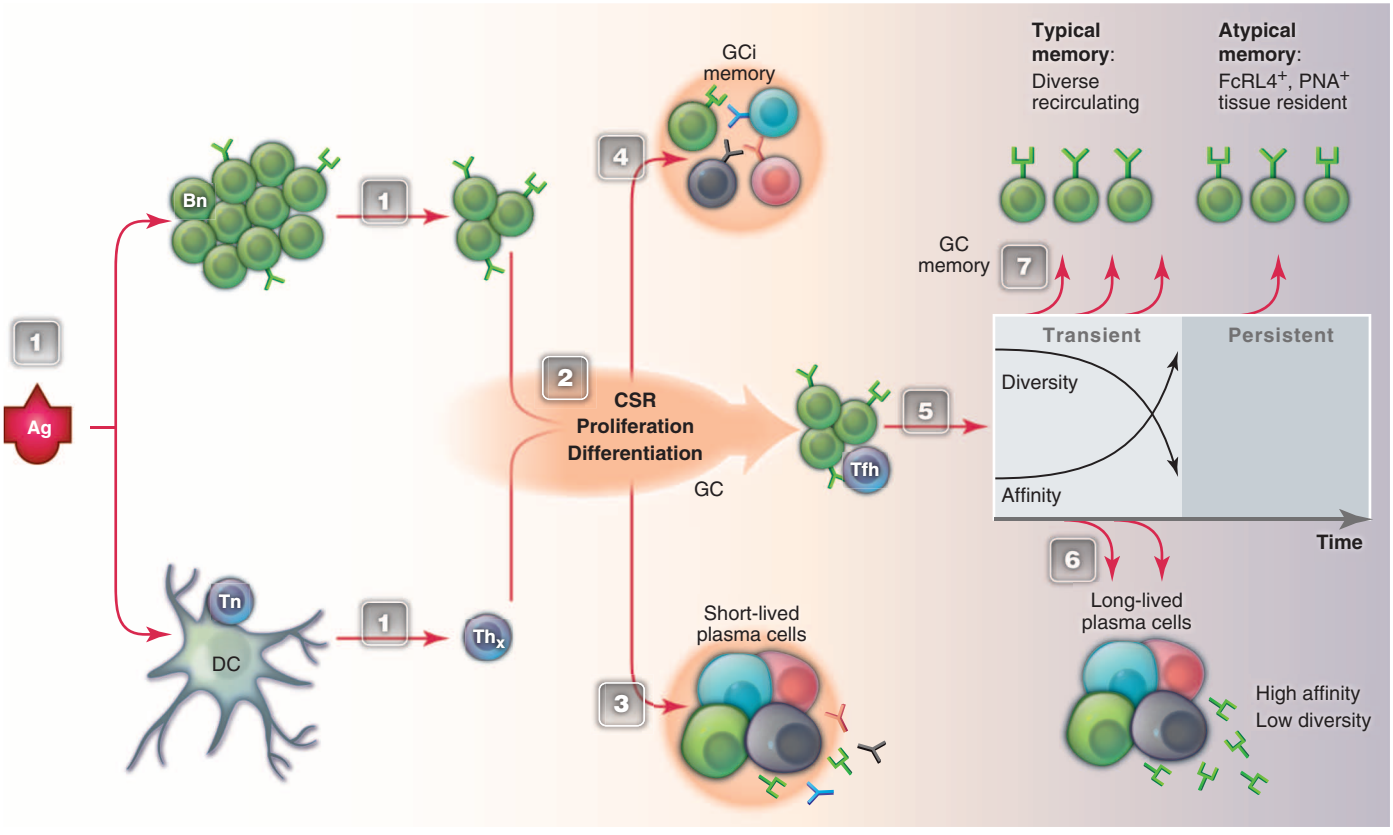


Fig. 3. Potential points of intervention to mold, shape, and influence humoral memory. (**1**) Altering the Ag to influence the number of B cells activated and the range of specificities included. Further, altering the programming of T cells at the beginning of the response—through modification of Ag or adjuvant or through small-molecule inhibitors of histone modifications to alter the expression of particular transcription factors—can alter the cytokine milieu that proceeds to instruct B cells. (**2**) The expansion of B cells at the time of CSR and before GC formation could be targeted through either the cytokine milieu (step 1) or genetic and epigenetic differences between subsets, altering the ratio of IgM to switched B cells. Increasing IgM memory, if this is where it originates, may increase the persistence of the population, whereas increasing the frequency of switched cells may increase switched memory able to differentiate to ASCs immediately in a subsequent infection. Additionally, inhibiting switching to isotypes that interfere with those that are protective (e.g., monomeric IgA inhibits IgG in HIV) or inhibiting pathogenic autoantibody isotypes (such as IgG2a) would be beneficial. (**3**) Modulating extrafollicular ASCs to avoid feedback inhibition of GCs or to increase the rapid production of protective antibodies. (**4**) GCi memory, possibly containing a broad spectrum of specificities for the immunizing antigen, could be harnessed for production of broadly reactive antibodies. (**5**) Controlling the entry of B cells and activity of T_{FH} cells in the GCs may address the balance between affinity improvements and diminishing clonal diversity. (**6**) Furthermore, controlling the duration of production of plasma cells from the GCs may substantially influence the composition of the LLPC compartment, as would control of their survival. (**7**) Enhancing the diversity of GC B cell specificities that are represented in the GC-derived memory B cell population may provide protection against a broad range of pathogens from immunization with a single type. Furthermore, regulating the balance of memory B cell (6) and plasma cell (7) production, potentially through epigenetic modulators, may assist in diseases characterized by overproduction of plasma cells (autoimmunity) and/or underproduction of memory B cells (immunodeficiencies). Finally, within the memory B cell compartment there appear to be different types of memory based on whether there is an acute response or whether there is a persistent response created either by multiple infections or persisting antigen. For example, in response to malaria, atypical memory B cells are produced that appear to be responsible for effective humoral responses, and thus understanding the factors involved in their formation could allow modulation of vaccines to entice their induction.

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identity and behavior. Cell surface ligands and receptors, soluble cytokines, and chemokines are important in regulating B cell behavior such as division, Ig isotype switching, and migration. Different pathogens, by programming specific cytokine patterns in antigen-specific T cells, instruct B cells to class-switch to particular isotypes, and this is mediated by transcription factors (Fig. 1). A landmark study from Coutelier *et al*. (*48*) assessed isotype production after different antigen challenges in mice. IgG2a dominated antiviral responses, whereas immunization with soluble proteins induced mainly IgG1. Furthermore, isotype switching in B cells is guided by cytokines with interferon-γ (IFN-γ) inducing switching to IgG2a, interleukin-4 (IL-4) switching to IgG1 and IgE, and transforming growth factor–β (TGF-β) switching to IgG2b and IgA (*52*). The cytokines produced by T cells, in turn, reflect T cell priming by the dendritic cells, themselves responding to innate signals of the immunizing antigen (Fig. 1).

Transcription factors induced by cytokines are essential in regulating B cell behavior (Fig. 1). For example, IL-4–induced NFIL3 is important for IgE transcription (*53*), and IFN-γ–induced T-box transcription factor expressed in T cells (T-bet) is an important regulator of switching to IgG2a (*54*) and of IgG2a$^+$ memory B cell formation and responses (*55*). Interestingly, induction and survival of IgG2a memory depends on T-bet, and IgA memory depends on Rorα, both acting through control of transcription of the BCR (*55*). During infection, cytokines are not induced in isolation, meaning several can be present at the same time. Therefore, B cells require the ability to integrate signals and respond effectively to each specific milieu. Because both IgG2a and IgA are important in responses to influenza, for example, the basis for segregation of flu reactivity into memory B cell subtypes associated with particular transcription factors after infection will be of great interest (Fig. 1). Thus, a key avenue for regulating isotype switching is through manipulating the cytokine milieu, possible through the antigen or the adjuvant, ultimately directing expression of particular transcription factors in the B cells (Fig. 3). This is important for vaccine efficacy, not only in matching Ig effector function with pathogen and with antibody distribution but also to avoid antibody interference. IgA, for example, has been reported to interfere with IgG function in several situations, including a recent study on HIV vaccines (*56*).

Not only is it important to fully delineate the molecular factors involved in formation of different memory subsets, it is also vital to reveal the intrinsic mechanisms underlying the differences in function. One investigative approach has been to interrogate genetic differences between IgM and switched memory B cells using human splenic subsets (*57*–*60*). Although changes in cell surface molecules and gene expression occur during a primary response, the transcriptional profile of memory B cells is remarkably similar to that of naïve B cells (*57*–*60*). Therefore, it is likely that differentiation into a memory B cell occurs without the large changes in transcriptional networks seen in GCs and PCs. However, memory B cells are Ag-experienced, and thus they may retain epigenetic memory of their previous involvement in an immune response. If so, the GC reaction may be a means of reprogramming gene expression in B cells and establishing through epigenetic marks a new, stable expression pattern in memory cells that is distinct from naïve cells. Differential histone modifications may, for example, be responsible for the remarkable longevity and stability of IgM memory B cells or may repress the cell cycle to allow rapid ASC differentiation of switched memory B cells.

Persistence of Memory B Cell Populations

Vaccine success is dependent on the longevity of LLPCs and memory B cells (Fig. 3). The persistence of LLPCs, which have a slow turnover and can survive in the absence of memory B cells (*61*–*63*), is dependent on continued expression of the prosurvival protein Mcl1 (*64*). This in turn depends on continued receipt of survival signals from surrounding cells that collectively constitute the plasma cell survival niche. Survival factors reported for LLPCs are many and include APRIL, IL-6, and CXCL12 produced by cells as diverse as eosinophils, stromal cells, and megakaryocytes (*65*–*67*). While loss of many cell types and factors affect LLPC survival, none have been shown to be essential to LLPC survival in the way Mcl1 is essential, suggesting a considerable, and not unexpected, degree of redundancy in this crucial function.

Bystander proliferation of the memory pool during infection, regardless of Ag specificity, was proposed as a means to repopulate stochastically the memory B cell compartments (*68*). Although this is an interesting hypothesis, other investigators have demonstrated that proliferation of memory B cells is exclusively Ag-dependent (*69*), indicating that this is unlikely to be a mechanism for memory maintenance. Exactly what is required, however, remains uncertain. Like LLPCs, memory B cells can persist in the absence of Ag-BCR signaling (*70*), T cell help (*71*), or input from precursors (*72*, *73*). While memory B cells up-regulate cell survival molecules such as Bcl2 (*57*) and are sensitive to their inhibition (*74*), there are likely to be additional, as yet unidentified factors driving self-renewal of the memory B cell populations. It is intriguing to note that Ag-specific IgM memory in mice persisted at near-peak frequency over a period during which IgG memory declined manyfold (*49*), suggesting that different survival mechanisms for different memory B cells may exist. Furthermore, for immunity to be maintained, mechanisms must exist to prevent the complete depletion of the memory B cell pool during secondary responses. The mechanisms underlying the bifunctionality of memory differentiation and maintenance are areas of intense research.

Mechanisms Underlying the Rapid and Robust Response of Memory B Cells

In response to previously seen pathogens, memory B cells rapidly differentiate into plasmablasts producing antibody capable of clearing the infection, far more quickly than during a primary response, which is the basis of vaccine success (*2*). Memory B cells have an intrinsic ability to enter division more quickly than naïve B cells (*57*), but the signaling mechanisms underlying their rapid and robust response remain unclear. A number of different approaches have been taken to investigate this question, including looking to Ig isotype for answers (*75*–*77*). Previously, the cytoplasmic tail of IgG, which had been shown to be important for the generation and signaling of IgG-expressing cells (*78*, *79*), was postulated to be responsible for the large number of plasmablasts generated during a memory response (*75*, *79*). Subsequently, enhanced signaling and proliferation of IgG- or IgE-expressing B cells was reported as due to recruitment of the adaptor protein Grb2 to phosphorylated tyrosines in their respective cytoplasmic tails (*77*). Additionally, the membrane proximal region of the IgG1 cytoplasmic tail has been reported to promote receptor clustering and signaling after antigen binding (*76*). However, although IgG signaling may enhance responsiveness, it is known that memory B cells can respond more rapidly and robustly than naïve B cells in the absence of stimulation through the BCR (*58*, *80*). Indeed human IgM and switched memory B cells are intrinsically poised to enter division earlier than naïve B cells, and this is correlated with the down-regulation of cell cycle inhibitors in resting memory B cells (*58*). Thus, intrinsic mechanisms other than or in addition to BCR signaling must underlie enhanced reactivation of memory B cells.

A mouse engineered to express IgG1 on naïve B cells has been used to provide insight into the role of IgG in secondary responses (*81*). Upon immunization, IgG1-naïve B cells behaved similarly to IgM naïve and not IgG1 memory in that IgG1-naïve B cells were biased toward differentiating into GC B cells and not plasmablasts. Thus, signaling through IgG alone cannot explain the altered responsiveness of memory B cells. The transcription factor Bach2 was expressed at lower amounts in IgG1 memory cells, which correlated with these cells favoring plasmablast differentiation over GC entry, whereas Bach2 was present at comparable levels in IgM- and IgG1-naïve B cells (*81*). It will be interesting to determine expression of Bach2 in IgM memory B cells as it may reveal a molecular mechanism for the propensity of those cells to enter GCs rather than differentiate into plasmablasts. Alternatively, if they down-regulate Bach2 similar to IgG1 memory B cells, then a novel mechanism may

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operate to prohibit IgM memory B cells from differentiating into plasmablasts.

Location of Persisting Memory B Cells

In contrast to LLPCs, which are found mainly in the bone marrow, spleen, and gut-associated lymphoid tissues, memory B cells can either be tissue-resident or recirculate through SLOs. Memory B cells have been found in the splenic marginal zone (*82*, *83*), mucosal epithelium (*84*), or next to contracting GCs within secondary lymphoid organs (*85*). In humans, a subset of tonsil-resident memory B cells has been described to express Fc receptor–like protein 4 (FcRL4) (*84*). This population, which has comparable levels of SHM and isotype switch to FcRL4-negative memory, fails to proliferate and instead is poised to secrete Ig (*84*). Two recent studies investigated the dispersion of memory B cells after intranasal infection of mice with influenza. Both IgG and IgA memory B cells could be found in the lung and draining lymph nodes (*86*, *87*), with the latter study finding these cells at least 5 months post-infection. IgA memory B cells were restricted to the responding tissues and to the blood, which may be in part due to up-regulation of the mucosal integrin α4β7 on IgA memory B cells (*88*), whereas IgG memory B cells were broadly dispersed among responding and nonresponding tissues (*86*, *87*). The differential localization of memory B cells based on isotype is of interest for vaccine development (Fig. 3), specifically for infections in which mucosal surfaces are a primary infection site.

Humoral Memory Generated in Acute Versus Chronic Infection

Potential differences in the functionality of the B cell memory pools arising in acute and chronic infections is an understudied area of memory B cell development that will be critical in generating new vaccines. B cells within the different memory populations may have different intrinsic requirements for their survival that may be related to their exposure to antigen—an acute versus a chronic or recurrent infection, for example. This may lead to differences in the half-life of memory B cell populations generated in response to different vaccines. Thus, fundamental differences in memory B cell populations dependent on the pathogen may be partly responsible for some vaccines requiring boosters, and others generating lifelong immunity. Indeed, in humans, persistent exposure to antigen has been shown to alter the composition of the memory B cell compartment. As discussed, a subset of tonsil-resident memory B cells express FcRL4. In malaria-infected (*89*) and HIV patients (*90*), so-called atypical, tissue-like memory B cells that express FcRL4 have been detected in increased numbers in peripheral blood. These cells express high levels of inhibitory receptors, and the role these receptors play in inhibiting function is beginning to be delineated (*91*, *92*). For instance, FcRL4 disrupts formation of the B cell immune synapse (the clustering of signaling and adhesion molecules on the cell surface that is essential for bi-directional signaling between antigen-presenting cells and lymphocytes) and blocks BCR signaling (*92*); conversely, silencing of FcRL4 by siRNA induces proliferation in response to BCR signaling (*91*). In the case of HIV, these memory cells can be induced to differentiate into ASCs that secrete antibody to HIV. As these antibodies are not present in the serum, however, these memory B cells are considered nonfunctional (*90*). Although found in healthy individuals (*84*), it was unclear until recently (i) whether tissue-resident cells differ from those found recirculating in increased numbers in malaria-infected and HIV-infected patients, (ii) whether it is the chronic presence of antigen (*93*) that increases the number of these cells, and (iii) whether this population subverts the memory B cell response so that it is inefficient at expanding and differentiating to secrete antibody to clear the infection. Recent evidence demonstrates that this population in fact can produce protective antibodies and that the chronic exposure to Ag, rather than leading to dysfunction of the memory population, induces increased numbers of atypical memory B cells (*94*). The evolution and role of this population, and other putative tissue-resident memory B cell subsets, in normal and disease settings is an area requiring more research. In sum, understanding how acute or persistent infections, and the microenvironments they produce, induce transcriptional and epigenetic modifications that underlie formation, persistence, and reactivation of different memory B cell subsets [identified by different isotypes and/or other cell surface molecules (*95*)], could lay the foundation for shaping the memory B cell population through vaccine design (Fig. 3).

Memory Repertoires: Congruent or Concentric?

The term "B cell memory" now encompasses both quiescent memory B cells and LLPCs, both generated during the primary response to antigen and both persisting for extended periods after clearance of the antigen. It is reasonable to ask what degree of overlap there is in the composition of these populations and, if they are not congruent, as there is reason to think, what basis there is for selective recruitment and what consequences might ensue. Although an exhaustive, systematic examination of the repertoire of antigen-specific B cells in the two compartments, which would be the most informative way to address this issue, has to our knowledge yet to be done, there are inferential studies in which the two memory populations have been examined that do provide some insight.

Studies with model antigens in mice examined affinity rather than specificity, due either to the restricted nature of the responding B cells (transgenic and therefore monoclonal for the BCR) or restricted by the immunizing antigen (a hapten) or both (*28*, *96*, *97*). These studies reported differences in affinity, with LLPCs being more stringently selected than memory cells (*28*, *96*), or timing, with LLPCs arising late in the GC process and memory B cells early (*97*).

The difference in reactivity between memory populations was confirmed in emphatic fashion by examining the immune response of mice to West Nile virus (*5*). In this case, antibody produced by LLPCs generated in the primary response was uniformly specific for a dominant, neutralizing determinant on the virus, with poor ability to block infection by variant viruses. The memory B cell compartment, however, did contain cells with reactivity to the variants, and some of these produced antibodies with higher affinity to the virus variant than to the inducing Ag, the hallmark of heteroclitic antibodies. Clearly, the memory B cell compartment had retained specificities that had not been recruited into the LLPC compartment. Although this may not be analogous to the simple hapten examples above, the conclusion is the same; the memory B cell population appears to retain greater diversity in antigen binding than the LLPC population. This may result in the retention of specificities that have considerable benefit to the host through an extended breadth of protection.

In humans, the repertoire of the memory B cell compartments has been assessed in several ways (*98*–*101*), but it remains difficult to directly compare the memory and bone-marrow LLPC repertoires of the same person. Despite this, there is evidence that these memory compartments differ in humans (*102*). Another way to examine this question in humans is to make use of an immune response—for example, influenza infection and vaccination. Patients infected with the pandemic H1N1 2009 influenza produced antibodies with rare, broadly neutralizing properties, antibodies that were not elicited by routine annual flu vaccination (*98*). Screening memory B cells taken from people before the appearance of the H1N1 2009 virus revealed such broadly neutralizing specificities among the existing flu memory B cells, specificities that conventional vaccination overwhelmingly failed to transfer into the LLPC compartment. Thus, specificities exist in the GC-derived, isotype-switched memory B cell compartment that are not duplicated in the LLPC compartment but that have protective potential and the retention of which may be considered evolutionarily advantageous. What is currently lacking, however, is a more systematic analysis of the repertoire of the various memory compartments to determine their interrelatedness, their relationship to the LLPCs, and their contributions to recall responses.

Conclusions and Prospects

We have attempted to describe the origins and functions of subsets of memory B cells that are

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Table 1. Properties of memory B cell subsets. Attributes of immunological memory segregate to some degree with isotype, and these are summarized here. Details are referenced in the text, except mutation of IgA memory B cells (*103*). PB, plasmablast.

	Classes of B cell memory in TD responses			
	IgM	IgG	IgA	LLPC
Germinal center	GC GCi?	GC GCi	GC GCi?	GC
Tissue tropism	Recirculating	Recirculating	Mucosal	BM mucosal
SHM	Nil/low	Nil/high	High	Low/high
Life span	Indefinite	Decays	Unknown	Indefinite
Reactivation	GC in low serum IgG	PB >> GC CSR	PB >> GC	Inert
Repertoire	Archival?	Broad	Unknown	Narrow

generated during T cell dependent immune responses (Table 1). The possibility that memory B cell responsiveness is differently partitioned between IgM and class-switched memory B cells, combined with the possibility that every response generates a memory B cell population that is representative of the pre-GC repertoire, means that there could exist among the multitude of memory cells generated in the response, every possible reactivity to the antigen. That is, careful examination of these compartments may reveal some to be archives of the B cell specificities that were possible, despite not necessarily being selected for during the amplification and commitment that occurs in the GCs. We speculate that this is especially the case for IgM memory that is independent of the GCs. Finally, when the criteria for formation and reactivation of specific memory B cell compartments is determined, we can consider guiding primary and recall responses by manipulating the composition of the antigen, the adjuvant, the cytokine milieu, and the duration of the response to maximize the benefit from immunization.

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Quantifying the Influence of Climate on Human Conflict

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Introduction: Despite the existence of institutions designed to promote peace, interactions between individuals and groups sometimes lead to conflict. Understanding the causes of such conflict is a major project in the social sciences, and researchers in anthropology, economics, geography, history, political science, psychology, and sociology have long debated the extent to which climatic changes are responsible. Recent advances and interest have prompted an explosion of quantitative studies on this question.

Methods: We carried out a comprehensive synthesis of the rapidly growing literature on climate and human conflict. We examined many types of human conflict, ranging from interpersonal violence and crime to intergroup violence and political instability and further to institutional breakdown and the collapse of civilizations. We focused on quantitative studies that can reliably infer causal associations between climate variables and conflict outcomes. The studies we examined are experiments or "natural experiments"; the latter exploit variations in climate over time that are plausibly independent of other variables that also affect conflict. In many cases, we obtained original data from studies that did not meet this criterion and used a common statistical method to reanalyze these data. In total, we evaluated 60 primary studies that have examined 45 different conflict data sets. We collected findings across time periods spanning 10,000 BCE to the present and across all major world regions.

Results: Deviations from normal precipitation and mild temperatures systematically increase the risk of conflict, often substantially. This relationship is apparent across spatial scales ranging from a single building to the globe and at temporal scales ranging from an anomalous hour to an anomalous millennium. Our meta-analysis of studies that examine populations in the post-1950 era suggests that the magnitude of climate's influence on modern conflict is both substantial and highly statistically significant ($P < 0.001$). Each 1-SD change in climate toward warmer temperatures or more extreme rainfall increases the frequency of interpersonal violence by 4% and intergroup conflict by 14% (median estimates).

Discussion: We conclude that there is more agreement across studies regarding the influence of climate on human conflict than has been recognized previously. Given the large potential changes in precipitation and temperature regimes projected for the coming decades—with locations throughout the inhabited world expected to warm by 2 to 4 SDs by 2050—amplified rates of human conflict could represent a large and critical social impact of anthropogenic climate change in both low- and high-income countries.

FIGURES AND TABLE IN THE FULL ARTICLE

Fig. 1. Samples and spatiotemporal resolutions of 60 studies examining intertemporal associations between climatic variables and human conflict.

Fig. 2. Empirical studies indicate that climatological variables have a large effect on the risk of violence or instability in the modern world.

Fig. 3. Examples of paleoclimate reconstructions that find associations between climatic changes and human conflict.

Fig. 4. Modern empirical estimates for the effect of climatic events on the risk of interpersonal violence.

Fig. 5. Modern empirical estimates for the effect of climatic events on the risk of intergroup conflict.

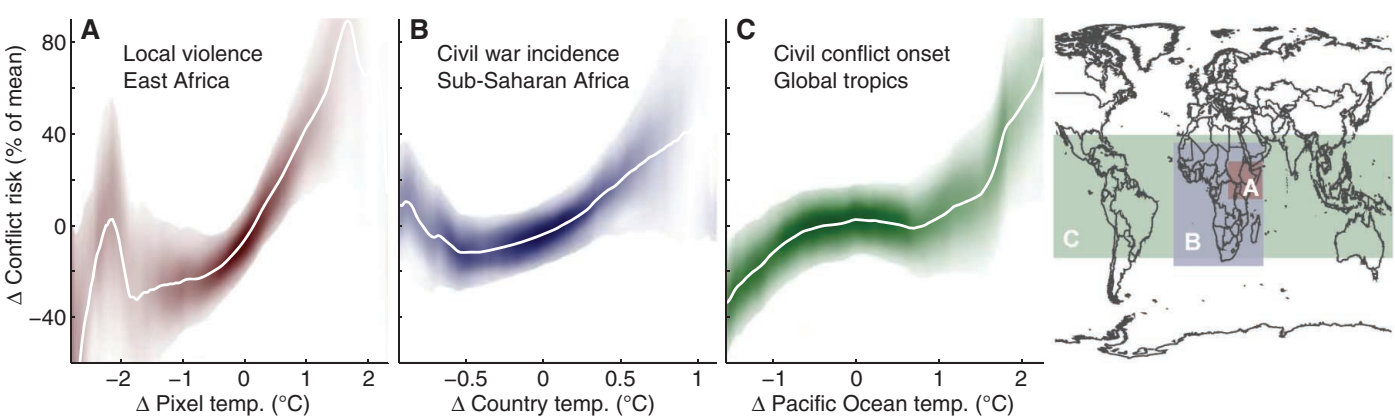
Fig. 6. Projected temperature change by 2050 as a multiple of the local historical SD (σ) of temperature.

Table 1. Primary quantitative studies testing for a relationship between climate and conflict, violence, or political instability.

SUPPLEMENTARY MATERIALS

Supplementary Text
Figs. S1 to S4
Tables S1 to S4
References (*140*, *141*)

Climate and conflict across spatial scales. Evidence that temperature influences the risk of modern human conflict: (**A**) local violence in 1° grid cells, (**B**) civil war in countries, and (**C**) civil conflict risk in the tropics. The map depicts regions of analysis corresponding to nonparametric watercolor regressions in (A) to (C). The color intensity in (A) to (C) indicates the level of certainty in the regression line.



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Quantifying the Influence of Climate on Human Conflict

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A rapidly growing body of research examines whether human conflict can be affected by climatic changes. Drawing from archaeology, criminology, economics, geography, history, political science, and psychology, we assemble and analyze the 60 most rigorous quantitative studies and document, for the first time, a striking convergence of results. We find strong causal evidence linking climatic events to human conflict across a range of spatial and temporal scales and across all major regions of the world. The magnitude of climate's influence is substantial: for each one standard deviation (1σ) change in climate toward warmer temperatures or more extreme rainfall, median estimates indicate that the frequency of interpersonal violence rises 4% and the frequency of intergroup conflict rises 14%. Because locations throughout the inhabited world are expected to warm 2σ to 4σ by 2050, amplified rates of human conflict could represent a large and critical impact of anthropogenic climate change.

Human behavior is complex, and despite the existence of institutions designed to promote peace, interactions between individuals and groups sometimes lead to conflict. When such conflict becomes violent, it can have dramatic consequences on human well-being. Mortality from war and interpersonal violence amounts to 0.5 to 1 million deaths annually (*1*, *2*), with nonlethal impacts, including injury and lost economic opportunities, affecting millions more. Because the stakes are so high, understanding the causes of human conflict has been a major project in the social sciences.

Researchers working across multiple disciplines including archaeology, criminology, economics, geography, history, political science, and psychology have long debated the extent to which climatic changes are responsible for causing conflict, violence, or political instability. Numerous pathways linking the climate to these outcomes have been proposed. For example, climatic changes may alter the supply of a resource and cause disagreement over its allocation, or climatic conditions may shape the relative appeal of using violence or cooperation to achieve some preconceived objective. Qualitative researchers have a well-developed history of studying these issues (*3*–*7*) dating back, at least, to the start of the 20th century (*8*). Yet, in recent years, growing recognition that the climate is changing, coupled with improvements in data quality and computing, has prompted an explosion of quantitative analyses seeking to test these theories and quantify the strength of these previously proposed linkages. Thus far, this work has remained scattered across multiple disciplines and has been difficult to synthesize given the disparate methodologies, data, and interests of the various research teams.

Here, we assemble the first comprehensive synthesis of this rapidly growing quantitative literature. We adopt a broad definition of "conflict," using the term to encompass a range of outcomes from individual-level violence and aggression to country-level political instability and civil war. We then collect all available candidate studies and, guided by previous criticisms that not all correlations imply causation (*9*–*11*), focus on only those quantitative studies that can reliably infer causal associations (*9*, *12*) between climate variables and conflict outcomes. The studies we examine exploit either experimental or natural-experimental variation in climate; the latter term refers to variation in climate over time that is plausibly independent of other variables that also affect conflict. To meet this standard, studies must account for unobservable confounding factors across populations, as well as for unobservable time-trending factors that could be correlated with both climate and conflict (*13*). In many cases, we obtained data from studies that did not meet this criterion and reanalyzed it with a common statistical model that did meet the criterion (see supplementary materials). The importance of this rigorous approach is highlighted by an example in which our standardized analysis generated findings consistent with other studies but at odds with the original conclusions of the study in question (*14*).

In total, we obtained 60 primary studies that either met this criterion or were reanalyzed with a method that met this criterion (Table 1). Collectively, these studies analyze 45 different conflict data sets published across 26 different journals and represent the work of more than 190 researchers from around the world. Our evaluation summarizes the recent explosion of research on this topic, with 78% of studies released since 2009 and the median study released in 2011. We collected findings across a wide range of conflict outcomes, time periods spanning 10,000 BCE to the present day, and all major regions of the world (Fig. 1).

Although various conflict outcomes differ in important ways, we find that the behavior of these outcomes relative to the climate system is markedly similar. Put most simply, we find that large deviations from normal precipitation and mild temperatures systematically increase the risk of many types of conflict, often substantially, and that this relationship appears to hold over a variety of temporal and spatial scales. Our meta-analysis of studies that examine populations in the post-1950 era suggests that these relationships continue to be highly important in the modern world, although there are notable differences in the magnitude of the relationship when different variables are considered: The standardized effect of temperature is generally larger than the standardized effect of rainfall, and the effect on intergroup violence (e.g., civil war) is larger than the effect on interpersonal violence (e.g., assault). We conclude that there is substantially more agreement and generality in the findings of this burgeoning literature than has been recognized previously. Given the large potential changes in precipitation and temperature regimes projected for the coming decades, our findings have important implications for the social impact of anthropogenic climate change in both low- and high-income countries.

Estimation of Climate-Conflict Linkages

Reliably measuring an effect of climatic conditions on human conflict is complicated by the inherent complexity of social systems. In particular, a central concern is whether statistical relationships can be interpreted causally or if they are confounded by omitted variables. To address this concern, we restrict our attention to studies with research designs that are scientific experiments or that approximate one (i.e., "natural experiments"). After describing how studies meet this criterion, we discuss how we interpret the precision of results, assess the importance of climatic factors, and address choices over functional form.

Research Design

In an ideal experiment, we would observe two identical populations, change the climate of one, and observe whether this treatment leads to more or less conflict relative to the control conditions. Because the climate cannot be experimentally manipulated, researchers primarily rely on natural experiments in which a given population is compared to itself at different moments in time when it is exposed to different climatic conditions—conditions that are exogenously determined by

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Table 1. Primary quantitative studies testing for a relationship between climate and conflict, violence, or political instability. "Stat. test" is Y if the analysis uses formal statistical methods to quantify the influence of climate variables and uses hypothesis testing procedures (Y, yes; N, no). "Large effect" is Y if the point estimate for the effect size is considered substantial by the authors or is greater in magnitude than 10% of the mean risk level for a 1σ change in climate variables. "Reject β = 0" is Y if the study rejects an effect size of zero at the 95% confidence level. "Reject β = 10%" is Y if the study is able to reject the hypothesis that the effect size is larger than 10% of the mean risk level for a 1σ change in climate variables. –, not applicable. SSA, sub-Saharan Africa; PDSI; Palmer Drought Severity Index; ENSO, El Niño–Southern Oscillation; NAO, North Atlantic Oscillation; N. Hem., Northern Hemisphere.

Study	Sample period	Sample region	Time unit	Spatial unit	Independent variable	Dependent variable	Stat. test	Large effect	Reject β = 0	Reject β = 10%	Ref.
Interpersonal conflict (15)											
Anderson *et al*. 2000*	1950–1997	USA	Annual	Country	Temp	Violent crime	Y	Y	Y	–	(*34*)
Auliciems *et al*. 1995†	1992	Australia	Week	Municipality	Temp	Domestic violence	Y	Y	Y	–	(*29*)
Blakeslee *et al*. 2013	1971–2000	India	Annual	Municipality	Rain	Violent and property crime	Y	Y	Y	–	(*42*)
Card *et al*. 2011†‡	1995–2006	USA	Day	Municipality	Temp	Domestic violence	Y	Y	Y	–	(*37*)
Cohn *et al*. 1997§	1987–1988	USA	Hours	Municipality	Temp	Violent crime	Y	Y	Y	–	(*30*)
Jacob *et al*. 2007†‖	1995–2001	USA	Week	Municipality	Temp	Violent and property crime	Y	Y	Y	–	(*35*)
Kenrick *et al*. 1986¶	1985	USA	Day	Site	Temp	Hostility	Y	Y	Y	–	(*27*)
Larrick *et al*. 2011†‡‖	1952–2009	USA	Day	Site	Temp	Violent retaliation	Y	Y	Y	–	(*36*)
Mares 2013	1990–2009	USA	Month	Municipality	Temp	Violent crime	Y	Y	Y	–	(*39*)
Miguel 2005†‡	1992–2002	Tanzania	Annual	Municipality	Rain	Murder	Y	Y	N	N	(*40*)
Mehlum *et al*. 2006	1835–1861	Germany	Annual	Province	Rain	Violent and property crime	Y	Y	Y	–	(*43*)
Ranson 2012†‖	1960–2009	USA	Month	County	Temp	Personal violence	Y	Y	Y	–	(*38*)
Rotton *et al*. 2000§	1994–1995	USA	Hours	Municipality	Temp	Violent crime	Y	Y	Y	–	(*31*)
Sekhri *et al*. 2013†	2002–2007	India	Annual	Municipality	Rain	Murder and domestic violence	Y	Y	Y	–	(*41*)
Vrij *et al*. 1994¶	1993	Netherlands	Hours	Site	Temp	Police use of force	Y	Y	Y	–	(*28*)
Intergroup conflict (30)											
Almer *et al*. 2012	1985–2008	SSA	Annual	Country	Rain/temp	Civil conflict	Y	Y	N	N	(*65*)
Anderson *et al*. 2013	1100–1800	Europe	Decade	Municipality	Temp	Minority expulsion	Y	Y	Y	–	(*63*)
Bai *et al*. 2010	220–1839	China	Decade	Country	Rain	Transboundary	Y	Y	Y	–	(*50*)
Bergholt *et al*. 2012‡#	1980–2007	Global	Annual	Country	Flood/storm	Civil conflict	Y	N	N	Y	(*75*)
Bohlken *et al*. 2011‖#	1982–1995	India	Annual	Province	Rain	Intergroup	Y	Y	N	N	(*44*)
Buhaug 2010#	1979–2002	SSA	Annual	Country	Temp	Civil conflict	Y	N	N	N	(*22*)
Burke 2012‡‖#	1963–2001	Global	Annual	Country	Rain/temp	Political instability	Y	Y	N**	N	(*71*)
Burke *et al*. 2009‡‖#††	1981–2002	SSA	Annual	Country	Temp	Civil conflict	Y	Y	Y	–	(*64*)
Cervellati *et al*. 2011	1960–2005	Global	Annual	Country	Drought	Civil conflict	Y	Y	Y	–	(*54*)
Chaney 2011	641–1438	Egypt	Annual	Country	Nile floods	Political Instability	Y	Y	Y	–	(*70*)
Couttenier *et al*. 2011#	1957–2005	SSA	Annual	Country	PDSI	Civil conflict	Y	Y	Y	–	(*53*)
Dell *et al*. 2012#	1950–2003	Global	Annual	Country	Temp	Political instability and civil conflict	Y	Y	Y	–	(*21*)
Fjelde *et al*. 2012‡#	1990–2008	SSA	Annual	Province	Rain	Intergroup	Y	Y	N**	N	(*55*)
Harari *et al*. 2013#	1960–2010	SSA	Annual	Pixel (1°)	Drought	Civil conflict	Y	Y	Y	–	(*52*)
Hendrix *et al*. 2012‡‖#	1991–2007	SSA	Annual	Country	Rain	Intergroup	Y	Y	Y	–	(*46*)
Hidalgo *et al*. 2010‡‖#	1988–2004	Brazil	Annual	Municipality	Rain	Intergroup	Y	Y	Y	–	(*25*)
Hsiang *et al*. 2011‖#	1950–2004	Global	Annual	World	ENSO	Civil conflict	Y	Y	Y	–	(*51*)
Jia 2012	1470–1900	China	Annual	Province	Drought/flood	Peasant rebellion	Y	Y	Y	–	(*56*)
Kung *et al*. 2012	1651–1910	China	Annual	County	Rain	Peasant rebellion	Y	Y	Y	–	(*47*)
Lee *et al*. 2013	1400–1999	Europe	Decade	Region	NAO	Violent conflict	Y	Y	Y	–	(*57*)
Levy *et al*. 2005‡‖#	1975–2002	Global	Annual	Pixel (2.5°)	Rain	Civil conflict	Y	Y	N**	N	(*49*)
Maystadt *et al*. 2013#	1997–2009	Somalia	Month	Province	Temp	Civil conflict	Y	Y	Y	–	(*66*)
Miguel *et al*. 2004#‡‡	1979–1999	SSA	Annual	Country	Rain	Civil war	Y	Y	Y	–	(*48*)
O'Laughlin *et al*. 2012‡‖#	1990–2009	E. Africa	Month	Pixel (1°)	Rain/temp	Civil/intergroup	Y	Y	Y	–	(*23*)
Salehyan *et al*. 2012	1979–2006	Global	Annual	Country	PDSI	Civil/intergroup	Y	Y	Y	–	(*76*)
Sarsons 2011	1970–1995	India	Annual	Municipality	Rain	Intergroup	Y	Y	Y	–	(*45*)
Theisen *et al*. 2011‡#	1960–2004	Africa	Annual	Pixel (0.5°)	Rain	Civil conflict	Y	N	N	N	(*24*)
Theisen 2012‡‖#	1989–2004	Kenya	Annual	Pixel (0.25°)	Rain/temp	Civil/intergroup	Y	Y	N**	N	(*14*)
Tol *et al*. 2009	1500–1900	Europe	Decade	Region	Rain/temp	Transboundary	Y	Y	Y	–	(*60*)
Zhang *et al*. 2007§§	1400–1900	N. Hem.	Century	Region	Temp	Instability	Y	Y	Y	–	(*59*)
Institutional breakdown and population collapse (15)											
Brückner *et al*. 2011#	1980–2004	SSA	Annual	Country	Rain	Inst. change	Y	Y	Y	–	(*78*)

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Study	Sample period	Sample region	Time unit	Spatial unit	Independent variable	Dependent variable	Stat. test	Large effect	Reject β = 0	Reject β = 10%	Ref.
Buckley *et al*. 2010‖‖	1030–2008	Cambodia	Decade	Country	Drought	Collapse	N	–	–	–	(*85*)
Büntgen *et al*. 2011‖‖	400 BCE–2000	Europe	Decade	Region	Rain/temp	Instability	N	–	–	–	(*62*)
Burke *et al*. 2010‡#	1963–2007	Global	Annual	Country	Rain/temp	Inst. change	Y	Y	Y	–	(*77*)
Cullen *et al*. 2000‖‖	4000 BCE–0	Syria	Century	Country	Drought	Collapse	N	–	–	–	(*83*)
D'Anjou *et al* 2012	550 BCE–1950	Norway	Century	Municipality	Temp	Collapse	Y	Y	Y	–	(*89*)
Ortloff *et al.* 1993‖‖	500–2000	Peru	Century	Country	Drought	Collapse	N	–	–	–	(*80*)
Haug *et al*. 2003‖‖	0–1900	Mexico	Century	Country	Drought	Collapse	N	–	–	–	(*84*)
Kelly *et al*. 2013	10050 BCE–1950	USA	Century	State	Temp/rain	Collapse	Y	Y	Y	–	(*88*)
Kennett *et al*. 2012	40 BCE–2006	Belize	Decade	Country	Rain	Collapse	N	–	–	–	(*87*)
Kuper *et al*. 2006	8000–2000 BCE	N. Africa	Millennia	Region	Rain	Collapse	N	–	–	–	(*81*)
Patterson *et al*. 2010	200 BCE–1700	Iceland	Decade	Country	Temp	Collapse	N	–	–	–	(*86*)
Stahle *et al*. 1998	1200–2000	USA	Multiyear	Municipality	PDSI	Collapse	N	–	–	–	(*82*)
Yancheva *et al*. 2007‖‖	2100 BCE–1700	China	Century	Country	Rain/temp	Collapse	N	–	–	–	(*79*)
Zhang *et al*. 2006	1000–1911	China	Decade	Country	Temp	Civil conflict and collapse	Y	Y	Y	–	(*58*)
				Number of studies (60 total):			**50**	**47**	**37**	**1**	
				Fraction of those using statistical tests:			**100%**	**94%**	**74%**	**2%**	

*Also see (*33*). †Shown in Fig. 4. ‡Reanalyzed using the common statistical model containing location fixed effects and trends (see supplementary materials). §Also see discussion in (*32*). ‖Shown in Fig. 2. ¶Actual experiment. #Shown in Fig. 5. **Effect size in the study is statistically significant at the 10% level, but not at the 5% level. ††Also see discussion in (*22*, *132*–*137*). ‡‡Also see discussion in (*138*, *139*). §§Also see (*61*). ‖‖Shown in Fig. 3.

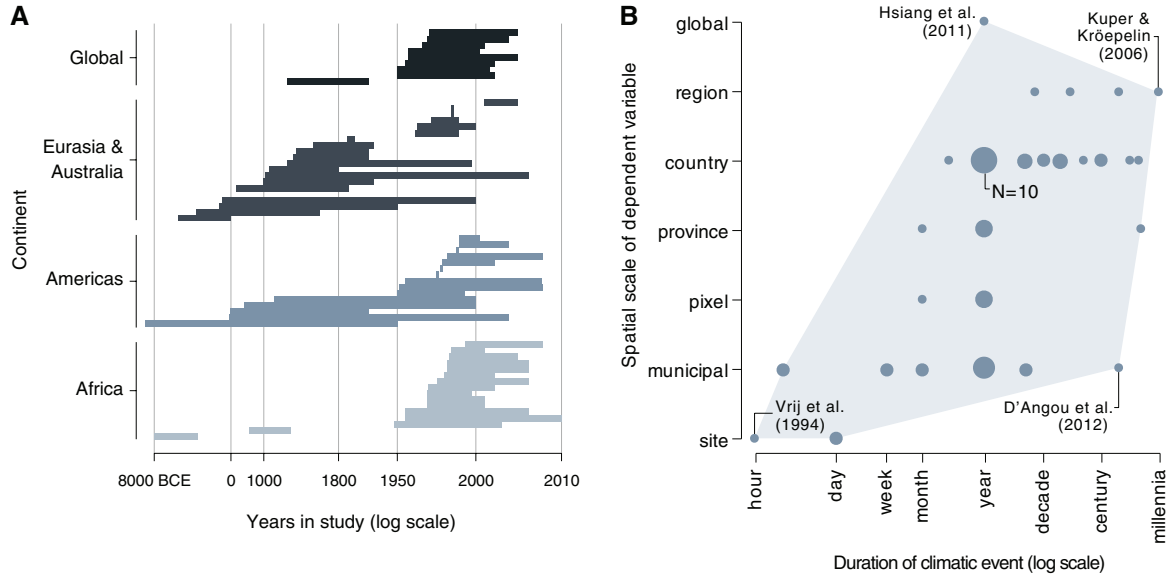


Fig. 1. Samples and spatiotemporal resolutions of 60 studies examining intertemporal associations between climatic variables and human conflict. (**A**) The location of each study region (*y* axis) plotted against the period of time included in the study (*x* axis). The *x* axis is scaled according to log years before the present but is labeled according to the year of the common era. (**B**) The level of aggregation in social outcomes (*y* axis) plotted against the time scale of climatic events (*x* axis). The envelope of spatial and temporal scales where associations are documented is shaded, with studies at extreme vertices labeled for reference. Marker size indicates the number of studies at each location, with the smallest bubbles marking individual studies and the largest bubble denoting 10 studies.

the climate system (*9*, *15*). In this research design, a single population serves as both the control population (e.g., just before a change in climatic conditions) and the treatment population (e.g., just after a change in climatic conditions). Thus, inferences are based only on how a fixed population responds to different climatic conditions that vary over time, and time-series or longitudinal analysis is used to construct a credible estimate for the causal effect of climate on conflict (*12*, *15*, *16*).

To minimize statistical bias and improve the comparability of studies, we focus on studies that use versions of the general model

$$conflict_variable_{it} = \beta \times climate_variable_{it} + \mu_i + \theta_t + \in_{it} \quad (1)$$

where locations are indexed by *i*, observational periods are indexed by *t*, β is the parameter of interest, and ∈ is the error. If different locations in a sample exhibit different average levels of conflict—perhaps because of cultural, historical, political, economic, geographic, or institutional differences between the locations—this will be accounted for by the vector of location-specific constants μ (commonly known as "fixed effects"). The vector of time-specific constants θ (a dummy for each time period) flexibly accounts for other time-trending variables such as economic growth or gradual demographic changes that could be correlated with both climate and conflict. In some cases, such as in time series, the θ_t parameters

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may be replaced by a generic trend (e.g., $\overline{\theta} \times t$) that is possibly nonlinear and is either common to all locations or may be location-specific (e.g., $\overline{\theta}_i \times t$). Our conclusions from the literature are based only on those studies that implement Eq. 1 or one of the mentioned alternatives. In select cases, when studies did not meet this criterion but the data from these analyses were publicly available or supplied by the authors, we used this common method to reanalyze the data (see supplementary materials). Many estimates of Eq. 1 in the literature and in our reanalysis account for temporal and/or spatial autocorrelation in the error term $\in$, although this adjustment was not considered a requirement for inclusion here. In the case of some paleoclimatological and archaeological studies, formal statistical analysis is not implemented because the outcome variables of interest are essentially singular cataclysmic events. However, we include these studies because they follow populations over time at a fixed location and are, thus, implicitly using the model in Eq. 1 (these cases are noted in Table 1).

We do not consider studies that are purely cross-sectional; that is, studies that only compare rates of conflict across different locations and attribute differences in average levels of conflict to average climatic conditions. Populations differ from one another in numerous ways (culture, history, etc.), many of them unobserved, and these "omitted variables" are likely to confound these analyses. In the language of the natural experiment, the treatment and control populations in these analyses are not comparable units, so we cannot infer whether a climatic treatment has a causal effect or not (*12*, *13*, *15*–*17*). For example, a cross-sectional study might compare average rates of civil conflict in Norway and Nigeria, attributing observed differences to the different climates of these countries, despite the fact that there are clearly many other relevant ways in which these countries differ. Nonetheless, some studies

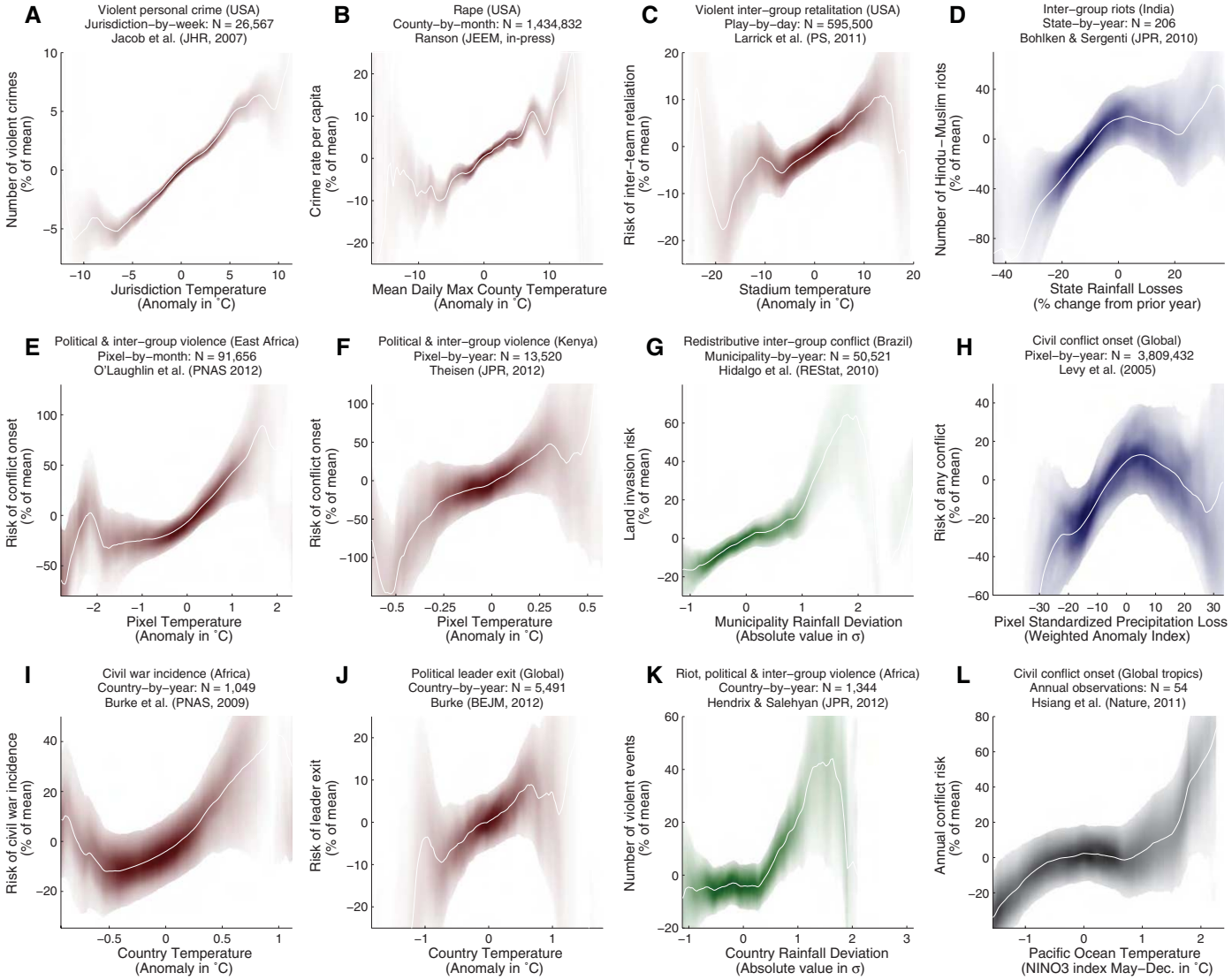


Fig. 2. Empirical studies indicate that climatological variables have a large effect on the risk of violence or instability in the modern world. (**A** to **L**) Examples from studies of modern data that identify the causal effect of climate variables on human conflict. Both dependent and independent variables have had location effects and trends removed, so all samples have a mean of zero. Relationships between climate and conflict outcomes are shown with nonparametric watercolor regressions, where the color intensity of 95% CIs depicts the likelihood that the true regression line passes through a given value (darker is more likely) (*128*). The white line in each panel denotes the conditional mean (*129*, *130*). Climate variables are indicated by color: red, temperature; green, rainfall deviations from normal; blue, precipitation loss; black, ENSO. Panel titles describe the outcome variable, location, unit of analysis, sample size, and study. Because the samples examined in each study differ, the units and scales change across each panel (see Figs. 4 and 5 for standardized effect sizes). "Rainfall deviation" represents the absolute value of location-specific rainfall anomalies, with both abnormally high and abnormally low rainfall events described as having a large rainfall deviation. "Precipitation loss" is an index describing how much lower precipitation is relative to the prior year's amount or the long-term mean.

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use cross-sectional analyses and attempt to control for confounding variables in regression analyses, typically using a handful of covariates such as average income or political indices. However, because the full suite of determinants of conflict is unknown and unmeasured, it is probably impossible that any cross-sectional study can explicitly account for all important differences between populations. Rather than presuming that all confounders are accounted for, the studies we evaluate compare Norway or Nigeria only to themselves at different moments in time, thereby ensuring that the structure, history, and geography of comparison populations are nearly identical.

Some studies implement versions of Eq. 1 that are expanded to explicitly control for potential confounding factors, such as average income. In many cases, this approach is more harmful than helpful because it introduces bias in the coefficients describing the effect of climate on conflict. This problem occurs when researchers control for variables that are themselves affected by climate variation, causing either (i) the signal in the climate variable of interest to be inappropriately

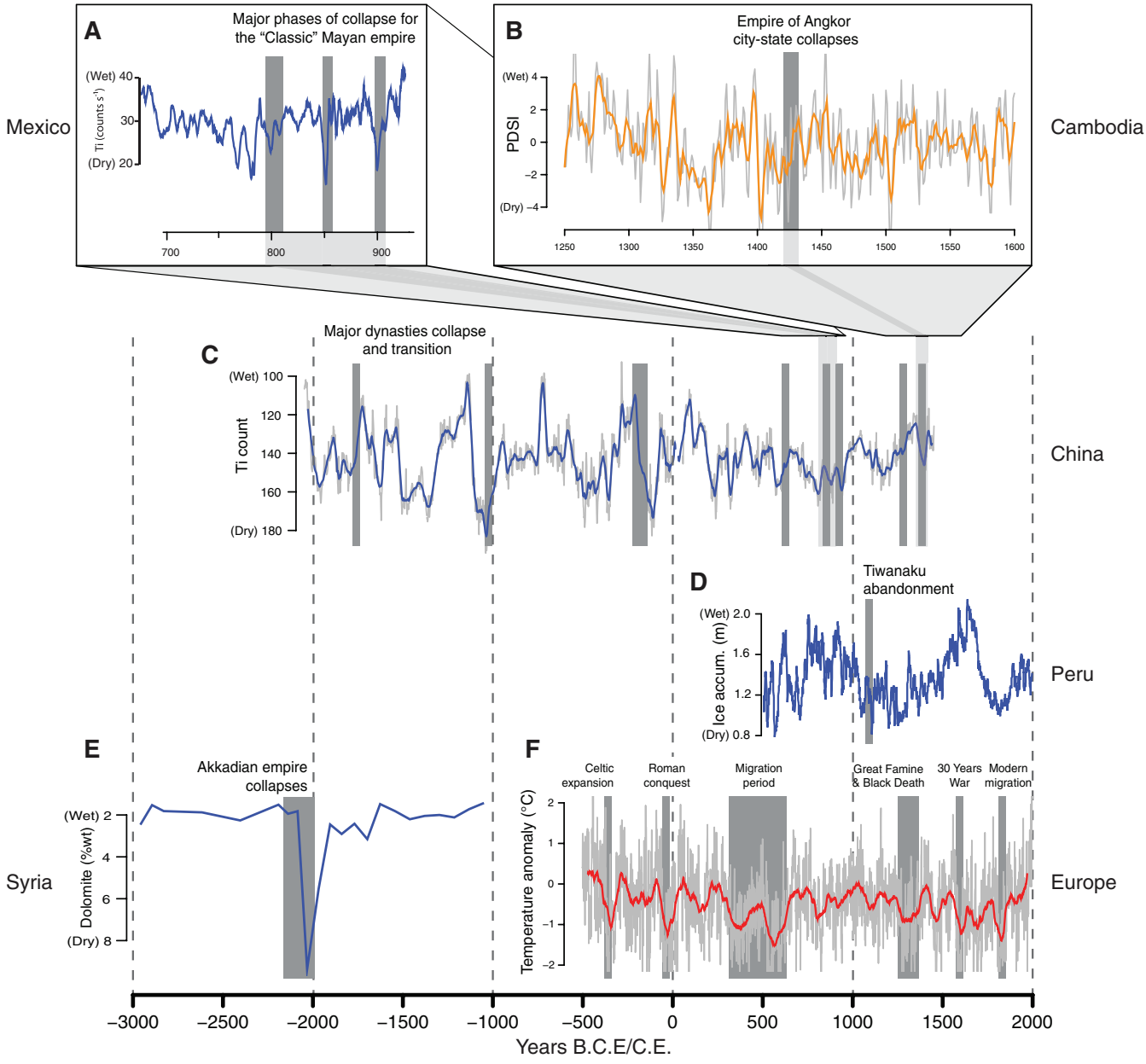


Fig. 3. Examples of paleoclimate reconstructions that find associations between climatic changes and human conflict. Lines are climate reconstructions (red, temperature; blue, precipitation; orange, drought; smoothed moving averages when light gray lines are shown), and dark gray bars indicate periods of substantial social instability, violent conflict, or the breakdown of political institutions. (**A**) Alluvial sediments from the Cariaco Basin indicate substantial multiyear droughts coinciding with the collapse of the Maya civilization (*84*). (**B**) Reconstruction of a drought index from tree rings in Vietnam, the Palmer drought severity index (PDSI), shows sustained megadroughts prior to the collapse of the Angkor kingdom (*85*). (**C**) Sediments from Lake Huguang Maar in China indicate abrupt and sustained periods of reduced summertime precipitation that coincided with most major dynastic transitions (*79*). The collapse of the Tang Dynasty (907) coincided with the terminal collapse of the Maya (A), both of which occurred when the Pacific Ocean altered rainfall patterns in both hemispheres (*79*). Similarly, the collapse of the Yuan Dynasty (1368) coincided with collapse of Angkor (B), which shares the same regional climate. (**D**) Tiwanaku cultivation of the Lake Titicaca region ended abruptly after a drying of the region, as measured by ice accumulation in the Quelccaya Ice Cap, Peru (*80*). (**E**) Continental dust blown from Mesopotamia into the Gulf of Oman indicates terrestrial drying that is coincident with the collapse of the Akkadian empire (*83*). (**F**) European tree rings indicate that anomalously cold periods were associated with major periods of instability on the European continent (*62*).

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absorbed by the control variable or (ii) the estimate to be biased because populations differ in unobserved ways that become artificially correlated with climate when the control variable is included. This methodological error is commonly termed "bad control" (*12*), and we exclude results obtained using this approach. The difficulty in this setting is that climatic variables affect many of the socioeconomic factors commonly included as control variables: things like crop production, infant mortality, population (via migration or mortality), and even political regime type. To the extent that these outcome variables are used as controls in Eq. 1, studies might draw mistaken conclusions about the relationship between climate and conflict. Because this error is so salient in the literature, we provide examples below. A full treatment can be found in (*12*, *18*).

For an example of (i), consider whether variation in temperature increases conflict. In many studies of conflict, researchers often employ a standard set of controls that are correlates of conflict, such as per capita income. However, evidence suggests that income is itself affected by temperature (*19*–*21*), so if part of the effect of temperature on conflict is through income, then controlling for income in Eq. 1 will lead the researcher to underestimate the role of temperature in conflict. This occurs because much of the effect of temperature will be absorbed by the income variable, biasing the temperature coefficient toward zero. At the extreme, if temperature influences conflict only through income, then controlling for income would lead the researcher in this example to draw exactly the wrong conclusion about the relationship between temperature and conflict: that there is no effect of temperature on conflict.

For an example of (ii), imagine that a measure of politics (i.e., democracy) and temperature both have a causal effect on conflict and both politics and temperature have an effect on income, but that income has no effect on conflict. If politics and temperature are uncorrelated, estimates of Eq. 1 that do not control for politics will still recover the unbiased effect of temperature. However, if income is introduced to Eq. 1 as a control but politics is left out of the model, perhaps because it is more difficult to measure, then there will appear to be an association between income and conflict because income will be serving as a proxy measure for politics. In addition, this adjustment to Eq. 1 also biases the estimated effect of temperature. This bias occurs because the types of countries that have high income when temperature is high are different, in terms of their average politics, from those countries that have high income when temperature is low. Thus, if income is held fixed as a control variable in a regression model, the comparison of conflict across temperatures is not an "apples-to-apples" comparison because politics will be systematically different across countries at different temperatures, generating a bias that can have either sign. In this example, the inclusion of income in the model leads to two incorrect conclusions: It biases the estimated relationship between climate and conflict and implicates income as playing a role in conflict when it does not.

Statistical Precision

We consider each study's estimated relationship between climate and conflict, as well as the estimate's precision. Because sampling variability and sample sizes differ across studies, some analyses present results that are more precise than other studies. Recognizing this fact is important when synthesizing a diverse literature, as some apparent differences between studies can be reconciled by evaluating the uncertainty in their findings. For example, some studies report associations that

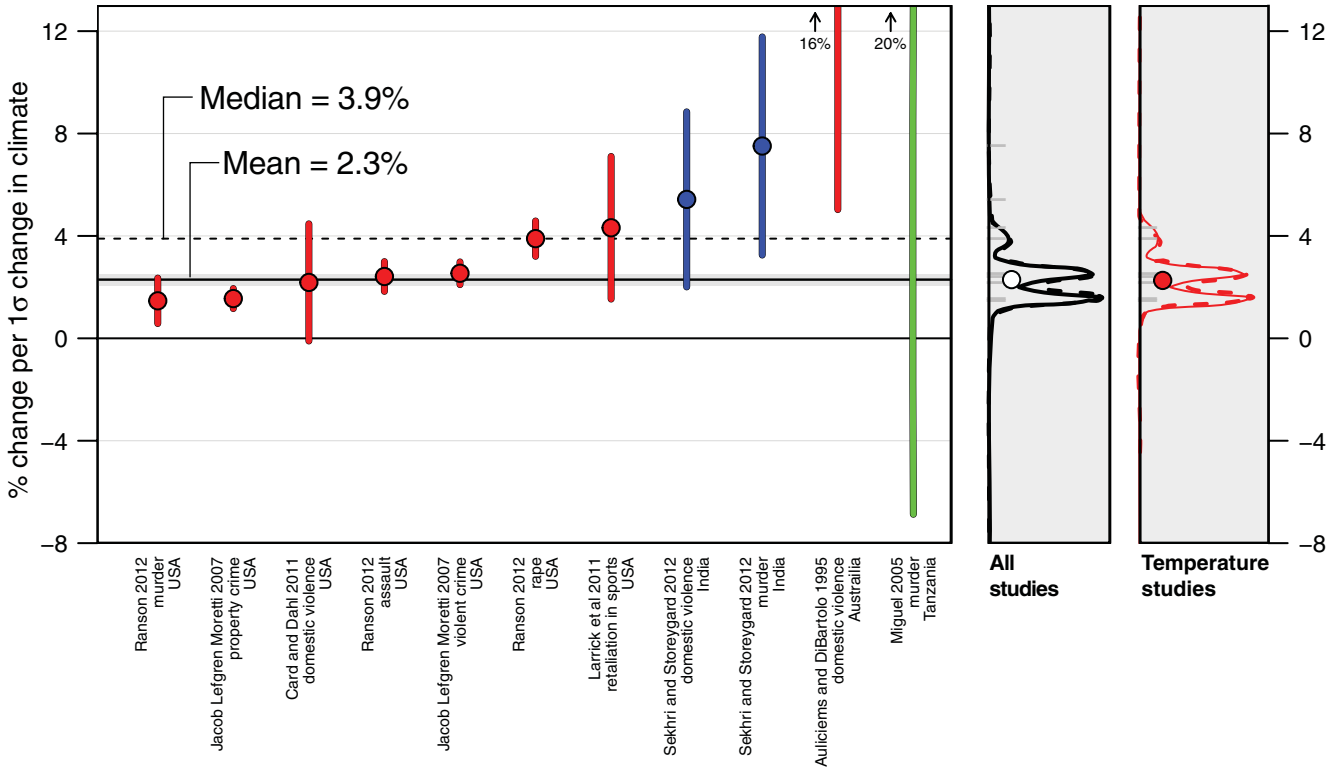


Fig. 4. Modern empirical estimates for the effect of climatic events on the risk of interpersonal violence. Each marker represents the estimated effect of a 1σ increase in a climate variable, expressed as a percentage change in the outcome variable relative to its mean. Whiskers represent the 95% CI on this point estimate. Colors indicate the forcing climate variable: A coefficient is positive if conflict increases with higher temperature (red), greater rainfall loss (blue), or greater rainfall deviation from normal (green). The dashed line indicates the median estimate; the top solid black line denotes the precision-weighted mean, with its 95% CI shown in gray. The panels on the right show the precision-weighted mean effect (circles) and the distribution of study results for all 11 results looking at individual conflict or for the subset of 8 results focusing on temperature effects. Distributions of effect sizes are either precision-weighted (solid lines) or derived from a Bayesian hierarchical model (dashed lines). See the supplementary materials for details on the individual studies and the calculation of mean effects and their distribution.

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are very large or very small but with uncertainties that are also very large, leading us to place less confidence in these extreme findings. This intuition is formalized in our meta-analysis, which aggregates results across studies by down-weighting results that are less precisely estimated.

The strength of a finding is sometimes summarized in a statement regarding its statistical significance, which describes the signal-to-noise ratio in an individual study. However, in principle, the signal is a relationship that exists in the real world and cannot be affected by the researcher, whereas the level of noise in a given study's finding (i.e., its uncertainty) is a feature specific to that study—a feature that can be affected by a researcher's decisions, such as the size of the sample they choose to analyze. Thus, although it is useful to evaluate whether individual findings are statistically significant and it is important to down-weight highly imprecise findings, individual studies provide useful information even when their findings are not statistically significant.

To summarize the evidence that each statistical study provides while also taking into account its precision, we separately consider three questions for each study in Table 1: (i) Is the estimated average effect of climate on conflict quantitatively "large" in magnitude (discussed below), regardless of its uncertainty? (ii) Is the reported effect large enough and estimated with sufficient precision that the study can reject the null hypothesis of "no relationship" at the 5% level? (iii) If the study cannot reject the hypothesis of "no relationship," can it reject the hypothesis that the relationship is quantitatively large? In the literature, often only the second question is evaluated in any single analysis. Yet, it is important to consider the magnitude of climate influence (first question) separately from its statistical precision,

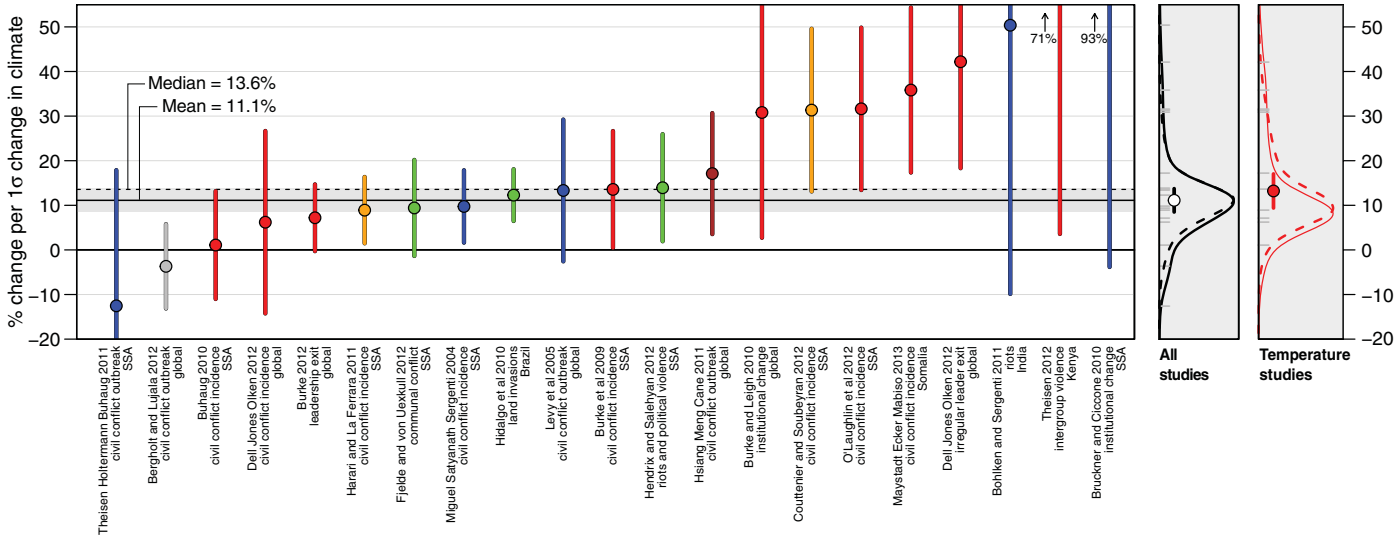


Fig. 5. Modern empirical estimates for the effect of climatic events on the risk of intergroup conflict. Each marker represents the estimated effect of a 1σ increase in a climate variable, expressed as a percentage change in the outcome variable relative to its mean. Whiskers represent the 95% CI on this point estimate. Colors indicate the forcing climate variable: A coefficient is positive if conflict increases with higher temperature (red), greater rainfall loss (blue), greater rainfall deviation from normal (green), more floods and storms (gray), more El Niño–like conditions (brown), or more drought (orange), as captured by different drought indices. The dashed line indicates the median estimate; the top solid black line denotes the precision-weighted mean, with its 95% CI shown in gray. The panels at right show the precision-weighted mean effect (circles) and the distribution of study results for all 21 results looking at intergroup conflict or for the subset of 12 results focusing on temperature effects (which includes the ENSO and drought studies). Distributions of effect sizes are either precision-weighted (solid lines) or derived from a Bayesian hierarchical model (dashed lines). See the supplementary materials for details on the individual studies and on the calculation of mean effects and their distribution.

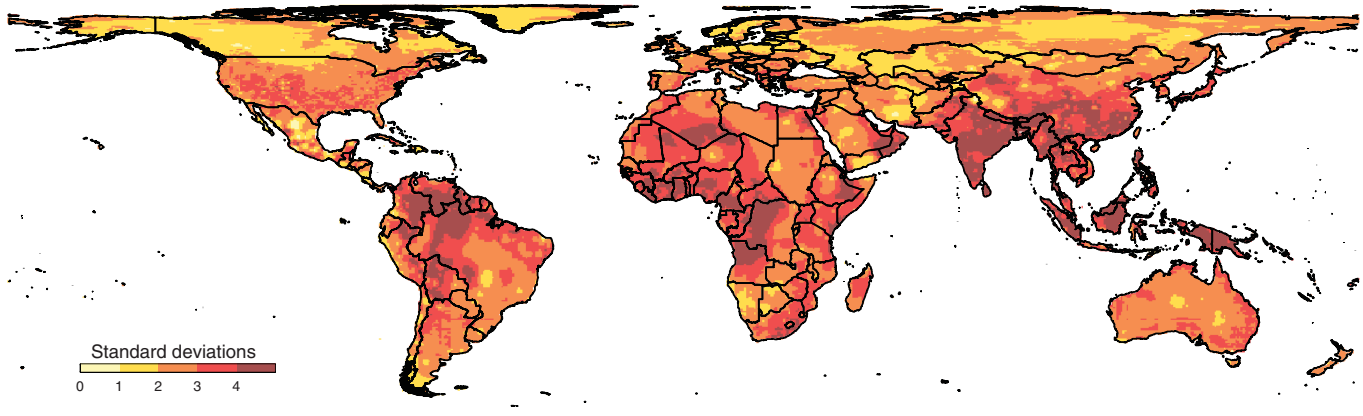


Fig. 6. Projected temperature change by 2050 as a multiple of the local historical SD (σ) of temperature. Temperature projections are for the A1B scenario and are averaged across 21 global climate models reporting in the Coupled Model Intercomparison Project (CMIP3) (*96*). Changes are the difference between projected annual average temperatures in 2050 and average temperatures in 2000. The historical SD of temperature is calculated from annual average temperatures at each grid cell over the period 1950–2008, using data from the University of Delaware (*131*). The map is an equal-area projection.

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because the magnitude of these effects tells us something about the potential importance of climate as a factor that may influence conflict, so long as we are mindful that evidence is weaker if a study's results are less certain. In cases in which the estimated effect is smaller in magnitude and not statistically different from zero, it is important to consider whether a study provides strong evidence of zero association—that is, whether the study rejects the hypothesis that an effect is large in magnitude (third question)—or relatively weak evidence because the estimated confidence interval (CI) spans large effects as well as zero effect.

Evaluating Whether an Effect Is Important

Evaluating whether an observed causal relationship is "important" is a subjective judgment that is not essential to our scientific understanding of whether there is a causal relationship. Nonetheless, because importance in this literature has sometimes been incorrectly conflated with statistical precision or inferred from incorrect interpretations of Eq. 1 and its variants, we explain our approach to evaluating importance.

Our preferred measure of importance is to ask a straightforward question: Do changes in climate cause changes in conflict risk that an expert, policy-maker, or citizen would consider large? To aid comparisons, we operationalize this question by considering an effect important if authors of a particular study state that the size of the effect is substantive, or if the effect is greater than a 10% change in conflict risk for each one SD (1σ) change in climate variables. This second criterion uses an admittedly arbitrary threshold, and other threshold selections would be justifiable. However, we contend that this threshold is relatively conservative, as most policy-makers or citizens would be concerned by effects well below 10% per 1σ. For instance, because random variation in a normally distributed climate variable lies in a 4σ range for 95% of its realizations, even a 3% per 1σ effect size would generate variation in conflict of 12% of its mean, which is probably important to those individuals experiencing these shifts.

In some prior studies, authors have argued that a particular estimated effect is unimportant based on whether a climatic variable substantially changes goodness-of-fit measures (e.g., R^2) for a particular statistical model, sometimes in comparison to other predictor variables (*14*, *22*–*24*). We do not use this criterion here for two reasons. First, goodness-of-fit measures are sensitive to the quantity of noise in a conflict variable: More noise reduces goodness of fit; thus, under this metric, irrelevant measurement errors that introduce noise into conflict data will reduce the apparent importance of climate as a cause of conflict, even if the effect of climate on conflict is quantitatively large. Second, comparing the goodness of fit across multiple predictor variables often makes little sense in many contexts, because (i) longitudinal models typically compare variables that predict both where a conflict will occur and when a conflict will occur, and (ii) these models typically compare the causal effect of climatic variables with the noncausal effects of confounding variables, such as endogenous covariates. These are "apples-to-oranges" comparisons, and the faulty logic of both types of comparison is made clear with examples.

For an example of (i), consider an analyst comparing violent crime over time in New York City and North Dakota who finds that the number of police on the street each day is important for predicting how much crime occurs on that day, but that a population variable describes more of the variation in crime because crime and population in North Dakota are both low. Clearly this comparison is not informative, because the reason that there is little crime in North Dakota has nothing to do with the reason why crime is lower in New York City on days when there are many police on the street. The argument that variations in climate are not important to predicting when conflict occurs because other variables are good predictors of where conflict occurs is analogous to the strange statement that the number of police in New York City is not important for predicting crime rates because North Dakota has lower crime that is attributable to its lower population.

For an example of (ii), suppose that both higher rainfall and higher household income lower the likelihood of civil conflict, but household income is not observed, and instead, a variable describing the average observable number of cars each household owns is included in the regression. Because wealthier households are better able to afford cars, the analyst finds that populations with more cars have a lower risk of conflict. This relationship clearly does not have a causal interpretation, and comparing the effect of car ownership on conflict with the effect of rainfall on conflict does not help us better understand the importance of the rainfall variable. Published studies that make similar comparisons do so with variables that the authors suggest are more relevant than cars, but the uninformative nature of comparisons between causal effects and noncausal correlations is the same.

Functional Form and Evidence of Nonlinearity

Some studies assume a linear relationship between climatic factors and conflict risk, whereas others assume a nonlinear relationship. Taken as a whole, the evidence suggests that, over a sufficiently large range of temperatures and rainfall levels, both temperature and precipitation appear to have a nonlinear relationship with conflict, at least in some contexts. However, this curvature is not apparent in every study, probably because the range of temperatures or rainfall levels contained within a sample may be relatively limited. Thus, most studies report only linear relationships that should be interpreted as local linearizations of a more complex, and possibly curved, response function.

As we will show, all modern analyses that address temperature impacts find that higher temperatures lead to more conflict. However, a few historical studies that examine temperate locations during cold epochs do find that abrupt cooling from an already cold baseline temperature may lead to conflict. Taken together, this collection of locally linear relationships indicates a global relationship with temperature that is nonlinear.

In studies of rainfall impacts, the distinction between linearity and curvature is made fuzzy by the multiple ways that rainfall changes have been parameterized in existing studies. Not all studies use the same independent variable, and because a simple transformation of an independent variable can change the response function from curved to linear and visa versa, it is difficult to determine whether results agree. In an attempt to make findings comparable, when replicating the studies that originally examine a nonlinear relationship between rainfall and conflict, we follow the approach of Hidalgo *et al*. (*25*) and use the absolute value of rainfall deviations from the mean as the independent variable. In studies that originally examined linear relationships, we leave the independent variable unaltered. Because these two approaches in the literature (and our reanalysis) differ, we make the distinction clear in our figures through the use of two different colors.

Results from the Quantitative Literature

We divide this section topically, examining, in turn, the evidence on how climatic changes shape personal violence, group-level violence, and the breakdown of social order and political institutions. Results from 12 example studies of recent data (post-1950) are displayed in Fig. 2. These findings were chosen to represent a broad cross section of outcomes, geographies, and time periods, and we used the common statistical framework described above to replicate these results (see supplementary materials). Findings from several studies of historical data are collected in Fig. 3, where the different time scales of climatic events can be easily compared. Table 1 lists and describes all primary studies. For a detailed description and evaluation of each individual study, see (*26*).

Personal Violence and Crime

Studies in psychology and economics have repeatedly found that individuals are more likely to exhibit aggressive or violent behavior toward others if ambient temperatures at the time of observation are higher (Fig. 2, A to C), a result that has been obtained in both experimental (*27*, *28*) and natural-experimental (*29*–*39*) settings. Documented aggressive behaviors that respond to temperature range from somewhat less consequential [e.g., horn-honking while driving (*27*) and interplayer violence during sporting events (*36*)] to much more serious [e.g., the use of force during police training (*28*), domestic violence within households (*29*, *37*), and violent crimes such as assault or rape (*30*–*35*, *38*)]. Although the physiological mechanism linking temperature to aggression remains unknown, the causal association appears robust across a variety of contexts. Importantly,

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because aggression at high temperature increases the likelihood that intergroup conflicts escalate in some contexts (*36*) and the likelihood that police officers use force (*28*), it is possible that this mechanism could affect the prevalence of group-level conflicts on a larger scale.

In low-income settings, extreme rainfall events that adversely affect agricultural income are also associated with higher rates of personal violence (*40*–*42*) and property crime (*43*). High temperatures are also associated with increased property crime (*34*, *35*, *38*), but violent crimes appear to rise with temperature more quickly than property crimes (*38*).

Group-Level Violence and Political Instability

Some forms of intergroup violence, such as Hindu-Muslim riots (Fig. 2D), tend to be more likely after extreme rainfall conditions (*44*–*47*). This relationship between intergroup violence and rainfall is primarily documented in low-income settings, suggesting that reduced agricultural production may be an important mediating mechanism, although alternative explanations cannot be excluded.

Low water availability (*23*, *46*, *48*–*57*), very low temperatures (*58*–*63*), and very high temperatures (*14*, *21*, *23*, *51*, *64*–*66*) have been associated with organized political conflicts in a variety of low-income contexts (Fig. 2, E, F, H, I, K, and L). The structure of this relationship again seems to implicate a pathway through climate-induced changes in income, either agricultural (*48*, *67*–*69*) or nonagricultural (*20*, *21*), although this hypothesis remains speculative. Large deviations from normal precipitation have also been shown to lead to the forceful reallocation of wealth (*25*) (Fig. 2G) or the nonviolent replacement of incumbent leaders (*70*, *71*) (Fig. 2J).

Some authors recently suggested that contradictory evidence is widespread among quantitative studies of climate and human conflict (*72*–*74*), but the level of disagreement appears overstated. Two studies (*22*, *24*) estimate that temperature and rainfall events have a limited impact on civil war in Africa, but the CIs around these estimates are sufficiently wide that they do not reject a relatively large effect of climate on conflict that is consistent with 35 other studies of modern data and 28 other studies of intergroup conflict. Within the broader literature of primary statistical studies, these results represent 4% of all reported findings (Table 1). Isolated studies also suggest that windstorms and floods have limited observable effect on civil conflicts (*75*) and that anomalously high rainfall is associated with higher incidence of terrorist attacks (*76*).

Institutional Breakdown

Under sufficiently high levels of climatological stress, preexisting social institutions may strain beyond recovery and lead to major changes in governing institutions (*77*–*79*) (Fig. 3C), a process that often involves the forcible removal of rulers. High levels of climatological stress have also led to major changes in settlement patterns and social organization (*80*, *81*) (Fig. 3D). Finally, in extreme cases, entire communities, civilizations, and empires collapse entirely after large changes in climatic conditions (*62*, *79*, *80*, *82*–*89*) (Fig. 3, A to C, E, and F). These documented catastrophic failures all precede the 20th century, yet the level of economic development in these communities at the time of their collapse was similar to the level of development in many poor countries of the modern world [see (*26*) for a comparison], an indicator that these historical cases may continue to have modern relevance.

Synthesis of Findings

Once attention is restricted to those studies able to make rigorous causal claims about the relationship between climate and conflict, some general patterns become clear. Here, we identify, for the first time, commonalities across results that span diverse social systems, climatological stimuli, and research disciplines.

Generality: Samples, Spatial Scales, and Rates of Climate Change

Social conflicts at all scales and levels of organization appear susceptible to climatic influence, and multiple dimensions of the climate system are capable of influencing these various outcomes. Studies documenting this relationship can be found in data samples covering 10,000 BCE to the present, and this relationship has been identified multiple times in each major region, as well as in multiple samples with global coverage (Fig. 1A).

Climatic influence on human conflict appears in both high- and low-income societies, although some types of conflict, such as civil war, are rare in high-income populations and do not exhibit a strong dependence on climate in those regions (*51*). Nonetheless, many other forms of conflict in high-income countries, such as violent crime (*35*, *38*), police violence (*28*), or leadership changes (*71*), do respond to climatic changes. These forms of conflict are individually less extreme, but their total social cost may be large because they are widespread. For example, during 1979–2009 there were more than 2 million violent crimes (assault, murder, and rape) per year on average in the United States alone (*38*), so small percentage changes can lead to substantial increases in the absolute number of these types of events.

Climatic perturbations at spatial scales ranging from a building (*27*, *28*, *36*) to the globe (*51*) have been found to influence human conflict or social stability (Fig. 1B). The finding that climate influences conflict across multiple scales suggests that coping or adaptation mechanisms are often limited. Interestingly, as shown in Fig. 1B, there is a positive association between the temporal and spatial scales of observational units in studies documenting a climate-conflict link. This might indicate that larger social systems are less vulnerable to high-frequency climate events, or it may be that higher-frequency climate events are more difficult to detect in studies examining outcomes over wide spatial scales.

Finally, it is sometimes argued that societies are particularly resilient to climate perturbations of a specific temporal scale: Perhaps these societies are capable of buffering themselves against short-lived climate events, or alternatively, they are able to adapt to conditions that are persistent. With respect to human conflict, the available evidence does not support either of these claims. Climatic anomalies of all temporal durations, from the anomalous hour (*28*) to the anomalous millennium (*81*), have been implicated in some form of human conflict (Fig. 1B).

The association between climatic events and human conflict is general in the sense that it has been observed almost everywhere: across types of conflict, human history, regions of the world, income groups, the various durations of climatic changes, and all spatial scales. However, it is not true that all types of climatic events influence all forms of human conflict or that climatic conditions are the sole determinant of human conflict. The influence of climate is detectable across contexts, but we strongly emphasize that it is only one of many factors that contribute to conflict [see (*90*) for a review of these other factors].

The Direction and Magnitude of Climatic Influence on Human Conflict

We must consider the magnitude of the climate's influence to evaluate whether climatic events play an important role in the occurrence of conflict and whether anthropogenic climate change has the potential to substantially alter future conflict outcomes. Quantifying the magnitude of climatic impact in archaeological and paleoclimatological studies is difficult because outcomes of interest are often one-off cataclysmic events (e.g., societal collapse), and we typically do not observe how the universe of societies would have responded to similar-sized shocks. Modern data samples, however, generally contain a large number of comparable social units (e.g., countries) that are repeatedly exposed to climatic variation, and this setting is more amenable to statistical analyses that quantify how changes in climate affect the risk of conflict within an individual social unit.

To compare quantitative results across studies of modern data, we computed standardized effect sizes for those studies where it was possible to do so, evaluating the effect of a 1σ change in the explanatory climate variable and expressing the result as a percentage change in the outcome variable. Because we restrict our attention to studies that examine changes in climate variables over time, the relevant SD is based only on intertemporal changes at each specific location instead of comparing variation in climate across different geographic locations.

Our results are displayed in Figs. 4 and 5 (colors match those in Figs. 2 and 3). Nearly all studies suggest that warmer temperatures, lower or more extreme rainfall, or warmer El Niño–Southern Oscillation (ENSO) conditions lead to a 2 to 40% increase in the conflict outcome per

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1σ in the observed climate variable. The consistent direction of temperature's influence is particularly notable because all 27 modern estimates (including ENSO and temperature-based drought indices, 20 estimates are shown in Figs. 4 and 5) indicate that warmer conditions generate more conflict, a result that would be extremely unlikely to occur by chance alone if temperature had no effect on conflict. It is more difficult to interpret whether the signs of rainfall-related variables agree because these variables are parameterized several different ways, so Figs. 4 and 5 present likelihoods for different parameterizations separately. However, if all modern rainfall estimates are pooled (including ENSO and rainfall-based drought indices, 13 estimates are shown in Figs. 4 and 5) using signs shown in Figs. 4 and 5, then the signs of the effects in 16 out of 18 estimates agree.

Under the assumption that there is some underlying similarity across studies, we compute the average effect of climate variables across studies by weighting each estimate according to its precision (the inverse of the estimated variance), a common approach that penalizes uncertain estimates (*91*). We also calculate the CI on this mean by assuming independence across studies, although this assumption is not critical to our central findings (in the supplementary materials, we present results where we relax this assumption and show that it is not essential). The precision-weighted average effect on interpersonal conflict is a 2.3% increase for each 1σ change in climatic variables (SE = 0.12%, $P < 0.001$; Fig. 4 and table S1) and the analogous estimate for intergroup conflict is 11.1% (SE = 1.3%, $P < 0.001$; Fig. 5 and table S1). These precision-weighted averages are relatively uninfluenced by outliers because outlier estimates in our sample tend to have low precision and, thus, low weight in the meta-analysis. The corresponding medians, which are also insensitive to outliers, are comparable: 3.9% for personal conflict and 13.6% for group conflict. If we restrict our attention to only the effects of temperature, the precision-weighted average effect is similar for interpersonal conflict (2.3%); however, for intergroup conflict, the effect rises to 13.2% per 1σ in temperature (SE = 2.0, $P < 0.001$; Fig. 5). Regarding the interpretation of these effect sizes, we note that whereas the average effect for interpersonal violence is smaller than the average effect for intergroup conflict in percentage terms, the baseline number of incidents of interpersonal violence is dramatically higher, meaning a small percentage increase can represent a substantial increase in total incidents.

We estimate the precision-weighted probability distribution of study-level effect sizes in Figs. 4 and 5 and in table S1. These distributions are centered at the precision-weighted averages described above and can be interpreted as the distribution of results from which studies' findings are drawn. The distribution for interpersonal conflict is narrow around its mean, probably because most interpersonal conflict studies focus on one country (the United States) and use very large samples and derive very precise estimates. The distribution for intergroup conflict is broader and covers values that are larger in magnitude, with an interquartile range of 6 to 14% per 1σ and the 5th to 95th percentiles spanning –5 to 32% per 1σ (table S1). We estimate that for the intergroup and interpersonal conflict studies, respectively, 10 and 0% of the probability mass of the distributions of effect sizes lies below zero.

Figures 4 and 5 make it clear that even though there is substantial agreement across results, some heterogeneity across estimates remains. It is possible that some of this variation is meaningful, perhaps because different types of climate variables have different impacts or because the social, economic, political, or geographic conditions of a society mediate its response to climatic events. For instance, poorer populations appear to have larger responses, consistent with prior findings that such populations are more vulnerable to climatic shifts (*51*). However, it is also possible that some of this variation is due to differences in how conflict outcomes are defined, measurement error in climate variables, or remaining differences in model specifications that we could not correct in our reanalysis.

To formally characterize the variation in estimated responses across studies, we use a Bayesian hierarchical model that does not require knowledge of the source of between-study variation (*92*) (see supplementary materials). Under this approach, estimates of the precision-weighted mean are essentially unchanged, and we recover estimates for the between-study SD (a measure of the underlying dispersion of true effect sizes across studies) that are half of the precision-weighted mean for interpersonal conflict and two-thirds of the precision-weighted mean for intergroup conflict (median estimates; see supplementary materials, fig. S3, and tables S2 and S3). By comparison, if variation in effect sizes across studies was driven by sampling variation alone, then this SD in the underlying distribution of effect sizes would be zero. This finding suggests that true effects probably differ across settings, and understanding this heterogeneity should be a primary goal of future research.

Publication Bias

Publication bias is a long-standing concern across the sciences, with a common form of bias arising from the research community's perceived preference for positive rather than null results. Although it is always possible that publication bias played a role in the publication of a specific analysis, there are multiple reasons why publication bias is unlikely to be driving our findings about the literature on climate and conflict. First, we include working papers in our analysis (as is common practice in the social sciences), thereby eliminating editorial selection. Second, the central results presented here are replicated in multiple disciplines and across diverse samples. Third, the large number of positive findings present in the literature since 2009 could provide limited professional incentive for researchers to publish yet another positive finding, and benefits might be higher to those who publish results with alternative findings. Fourth, many analyses are not explicitly focused on the direct effect of climate on conflict but instead use climatic variations instrumentally (*25*, *35*, *48*, *71*, *77*) or account for it as an ancillary covariate in their analysis [e.g., (*37*)] while trying to study a different research question, indicating that these authors have little professional stake in the sign, magnitude, or statistical significance of the climatic effects they are presenting. Fifth, we reanalyze the raw data from many studies using a common statistical framework, possibly undoing adjustments that authors might be making to their analysis (consciously or unconsciously) that make their findings appear stronger. Partial support for this idea is provided by individual studies that present significant results, but whose results are only marginally significant or no longer significant after our reanalysis (see supplementary materials for details). Finally, we look for evidence of publication bias by examining whether the statistical strength of individual studies reflects their sample size (*93*) and do not find systematic evidence of strong bias in absolute terms or in comparison to other social science literature (see fig. S4, table S4, and supplementary materials).

Implications for Future Climatic Changes

The above evidence, taken at face value, makes the case that future anthropogenic climate change could worsen conflict outcomes across the globe in comparison to a future with no climatic changes, given the large expected increase in global surface temperatures and the likely increase in variability of precipitation across many regions over coming decades (*94*, *95*). Recalling our finding that a 1σ change in a location's temperature is associated with an average 2.3% increase in the rate of interpersonal conflict and a 13.2% increase in the rate of intergroup conflict, and assuming that future populations will respond to climatic shifts similarly to how current populations respond, one can consider the potential effect of anthropogenic warming by rescaling expected temperature changes according to each location's historical variability. Although not all conflict outcomes have been shown to be responsive to changes in temperature, many have, and the results uniformly indicate that increasing temperatures are harmful in regions that are temperate or warm initially. In Fig. 6, we plot expected warming by 2050, computed as the ensemble mean for 21 climate models running the A1B emissions scenario, in terms of location-specific SDs (*96*). Almost all inhabited locations warm by >2σ, with the largest increases exceeding 4σ in tropical regions that are already warm and currently experience relatively low interannual temperature variability. These large climatological changes, combined with the quantitatively large effect of climate on conflict—particularly intergroup conflict—suggest

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that amplified rates of human conflict could represent a large and critical impact of anthropogenic climate change

Two reasons are often given as to why climate change might not have a substantive impact on human conflict: Future climate change will occur gradually and will, thus, allow societies to adapt, and the modern world today is less susceptible to climate variation than it has been in the past. However, if slower-moving climate shocks have smaller effects, or if the world has become less climate-sensitive, it is unfortunately not obvious in the data. Gradual climatic changes appear to adversely affect conflict outcomes, and the majority of the studies we review use a sample period that extends into the 21st century (recall Fig. 1). Furthermore, some studies explicitly examine whether populations inhabiting hotter climates exhibit less conflict when hot events occur but find little evidence that these areas are more adapted (*31*, *38*). We also note that many of the modern linkages between high-temperature anomalies and intergroup conflict have been characterized in Africa (*14*, *23*, *52*, *64*, *66*) or the global tropics and subtropics (*21*, *51*), regions with hot climates where we would expect populations to be best adapted to high temperatures. Nevertheless, it is always possible that future populations will adapt in previously unobserved ways, but it is impossible to know if and to what extent these adaptations will make conflict more or less likely.

Studies of nonconflict outcomes do indicate that, in some situations, historical adaptation to climate is observable, albeit costly (*97*–*100*), whereas in other cases there is limited evidence that any adaptation is occurring (*19*, *101*). To our knowledge, no study has characterized the scale or scope for adaptation to climate in terms of conflict outcomes, and we believe this is an important area for future research. Given the quantitatively large effect of climate on conflict, future adaptations will need to be dramatic if they are to offset the potentially large amplification of conflict.

Future Research

Given the marked consistency of available quantitative evidence linking climate and conflict, in our view, the top research priority in this field should be to narrow the number of competing explanatory hypotheses. Beyond efforts to mitigate future warming, limiting climate's future influence on conflict requires that we understand the causal pathways that generate the observed association. This task is made difficult by the likely situation that multiple mechanisms contribute to the observed relationships and that different mechanisms dominate in different contexts. The rich qualitative literature (*3*–*7*) suggests that a multiplicity of mechanisms may be at work.

To date, no study has been able to conclusively pin down the full set of causal mechanisms, although some studies find suggestive evidence that a particular pathway contributes to the observed association in a particular context. In most cases, this is accomplished by "fingerprinting" the effect of climate on an intermediary variable, such as income, and showing that the same statistical fingerprint is visible in the climate's effect on conflict. This approach, typically called "instrumental variables" (*12*) in the social sciences, identifies a mechanism linking climate and conflict under the assumption that climate's only influence on conflict is through the particular intermediate variable in question. Because this assumption is often difficult or impossible to test, evidence from this approach is more suggestive than conclusive in uncovering mechanisms (*51*).

An alternate and promising research design that can help rule out certain hypotheses is to study situations in which plausibly exogenous events block a proposed pathway in a treated subpopulation and then to compare whether the climate-conflict association persists or disappears in both the treatment and control subpopulations. In an example of this approach, Sarsons examines whether rainfall shortages in India lead to riots because they depress local agricultural income (*45*). By showing that rainfall shortages and riots continue to occur together in districts with dams that supply irrigation, investments that partially decouple local agricultural income from temporary rain shortfalls, Sarsons argues that the rainfall effect on riots is unlikely to be operating solely through changes in local agricultural income.

Plausible Mechanisms

The following hypotheses have, in our judgment, received the strongest empirical support in existing analyses, although the evidence is still often inconclusive. A common hypothesis focuses on local economic conditions and labor markets and argues that when climatic events cause economic productivity to decline (*19*–*21*, *68*, *69*, *102*–*104*), the value of engaging in conflict is likely to rise relative to the value of participating in normal economic activities (*48*, *52*, *105*–*110*). A competing hypothesis on state capacity argues that these declines in economic productivity reduce the strength of governmental institutions (e.g., if tax revenues fall), curtailing their ability to suppress crime and rebellion or encouraging competitors to initiate conflict during these periods of relative state weakness (*61*, *70*, *71*, *77*–*79*, *84*, *85*).

A second set of hypotheses focuses on what have, more generally, been termed "grievances." Hypotheses about inequality contend that when climatic events increase actual (or perceived) social and economic inequalities in a society (*111*, *112*), this could increase conflict by motivating attempts to redistribute assets (*25*, *34*, *35*, *43*). Evidence linking changes in food prices to conflict (*61*, *113*–*115*) can be interpreted similarly—for example, food riots due to a government's perceived inability to keep food affordable—particularly when some members of society can influence food markets (*111*, *116*).

Climate-induced migration and urbanization might also be implicated in conflict. If climatic events cause large population displacements or rapid urbanization (*97*, *117*, *118*,), this might lead to conflicts over geographically stationary resources that are unrelated to the climate (*119*) but become relatively scarce where populations concentrate. Changes in climate might also affect the logistics of human conflict (*76*, *120*), for example, by altering the physical environment (e.g., road quality) in which disputes or violence might occur (*52*, *120*, *121*). Finally, climate anomalies might result in conflict because they can make cognition and attribution more difficult or error-prone, or they may affect aggression through some physiological mechanism. For instance, climatic events may alter individuals' ability to reason and correctly interpret events (*27*, *28*, *30*, *31*, *34*–*36*), possibly leading to conflicts triggered by misunderstandings. Alternatively, if climatic changes and their economic consequences are inaccurately attributed to the actions of an individual or group (*63*, *122*–*125*)—for example, an inept political leader (*71*)—this may lead to violent actions that try to return economic conditions to normal by removing the "offending" population.

Selecting Climate Variables and Conflict Outcomes

Climate variables that have been analyzed previously, such as seasonal temperatures, precipitation, water availability indices, and climate indices, may be correlated with one another and autocorrelated across both time and space. For instance, temperature and precipitation time series tend to be negatively correlated in much of the tropics, and drought indices tend to be spatially correlated (*51*, *126*). Unfortunately, only a few of the existing studies account for the correlations between different variables, so it may be that some studies mistakenly measure the influence of an omitted climate variable by proxy [see (*126*) for a complete discussion of this issue]. Except for the experiments linking temperature to aggression (*27*, *28*), only a few studies demonstrate that a specific climate variable is more important for predicting conflict than other climate variables or that climatic changes during a specific season are more important than during other seasons. Furthermore, no study isolates a particular type of climatic change as the most influential, and no study has identified whether temporal or spatial autocorrelations in climatic variables are mechanistically important. Identifying the climatic variables, timing of events, and forms of autocorrelation that influence conflict will help us better understand the mechanisms linking climatic changes to conflict.

A similar situation exists with the choice of conflict outcomes. Most analyses simply document changes in the rate at which conflicts are reported in aggregate, but this approach provides only limited insight into how the evolution of conflict is affected by climatic variables. A path for future investigation is to link climate data

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with richer conflict data that describes different stages of the conflict "life cycle." For example, future studies could examine how often nonviolent group disputes become violent. Two studies cited in this paper (*28*, *36*) demonstrate the usefulness of selecting conflict variables other than total conflict rates. By examining the probability that an initial confrontation escalates rather than just counting the total number of conflicts, these studies demonstrate that high temperatures lead to more violence by increasing the likelihood that a small conflict escalates into a larger conflict.

Conclusion

Findings from a growing corpus of rigorous quantitative research across multiple disciplines suggest that past climatic events have exerted considerable influence on human conflict. This influence appears to extend across the world, throughout history, and at all scales of social organization. We do not conclude that climate is the sole, or even primary, driving force in conflict, but we do find that when large climate variations occur, they can have substantial effects on the incidence of conflict across a variety of contexts. The median effect of a 1σ change in climate variables generates a 14% change in the risk of intergroup conflict and a 4% change in interpersonal violence, across the studies that we review where it is possible to calculate standardized effects. If future populations respond similarly to past populations, then anthropogenic climate change has the potential to substantially increase conflict around the world, relative to a world without climate change.

Although there is marked convergence of quantitative findings across disciplines, many open questions remain. Existing research has successfully established a causal relationship between climate and conflict but is unable to fully explain the mechanisms. This fact motivates our proposed research agenda and urges caution when applying statistical estimates to future warming scenarios. Importantly, however, it does not imply that we lack evidence of a causal association. The studies in this analysis were selected for their ability to provide reliable causal inferences and they consistently point toward the existence of at least one causal pathway. To place the state of this research in perspective, it is worth recalling that statistical analyses identified the smoking of tobacco as a proximate cause of lung cancer by the 1930s (*127*), although the research community was unable to provide a detailed account of the mechanisms explaining the linkage until many decades later. So although future research will be critical in pinpointing why climate affects human conflict, disregarding the potential effect of anthropogenic climate change on human conflict in the interim is, in our view, a dangerously misguided interpretation of the available evidence.

Numerous competing theories have been proposed to explain the linkages between the climate and human conflict, but none have been convincingly rejected, and all appear to be consistent with at least some existing results. It seems likely that climatic changes influence conflict through multiple pathways that may differ between contexts, and innovative research to identify these mechanisms is a top research priority. Achieving this research objective holds great promise, as the policies and institutions necessary for conflict resolution can be built only if we understand why conflicts arise. The success of such institutions will be increasingly important in the coming decades, as changes in climatic conditions amplify the risk of human conflicts.

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Supplementary Materials

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Supplementary Text
Figs. S1 to S4
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From Cosmology to Cold Atoms: Observation of Sakharov Oscillations in a Quenched Atomic Superfluid

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Predicting the dynamics of many-body systems far from equilibrium is a challenging theoretical problem. A long-predicted phenomenon in hydrodynamic nonequilibrium systems is the occurrence of Sakharov oscillations, which manifest in the anisotropy of the cosmic microwave background and the large-scale correlations of galaxies. Here, we report the observation of Sakharov oscillations in the density fluctuations of a quenched atomic superfluid through a systematic study in both space and time domains and with tunable interaction strengths. Our work suggests a different approach to the study of nonequilibrium dynamics of quantum many-body systems and the exploration of their analogs in cosmology and astrophysics.

Sakharov oscillations (*1*, *2*), conventionally discussed in the context of early universe evolution and the anisotropy of cosmic microwave background (CMB) radiation (*3*–*9*), are a consequence of the interference of acoustic waves synchronously generated in an ideal fluid. Notably, the oscillations are insensitive to the microscopic details of the medium and can potentially be observed in laboratory conditions (*10*). In atomic superfluids, long-wavelength excitations are described by the hydrodynamic propagation of phonons (*11*), which provides the underpinning of many intriguing proposals (*12*–*16*) and experiments (*17*, *18*) to explore cosmology and black hole physics with nonequilibrium evolution of atomic quantum gases.

In Sakharov oscillations, synchronously generated acoustic waves interfere as time evolves, and the sound speed v relates the time and length scales of the interference. Let us assume that two counter-propagating waves with momenta $\hbar k$ and $-\hbar k$ are created with a relative phase ϕ, where $2\pi\hbar$ is the Planck constant. After a propagation time τ, the waves interfere constructively if their phases satisfy the relationship $2kv\tau + \phi = 2l\pi$, or destructively if $2kv\tau + \phi = 2(l - 1/2)\pi$, where $l = 1,2,3\ldots$ is an integer. Notably, $k_c = \pi/v\tau$ defines the sonic horizon, and Sakharov oscillations occur within the sound cone ("subhorizon regime") $k > k_c$. Outside the sound cone ("superhorizon regime") $k < k_c$, waves do not overlap and thus do not interfere (*8*). The sound cone thus defines a boundary within which correlations can propagate, in close analogy with the light cone discussed in relativity.

Here, we report the observation of Sakharov oscillations in quenched atomic superfluids. To synchronously generate sound waves, we quench the atomic interactions by Feshbach tuning (*19*) to different values. The waves that are created are in phase temporally, and are randomly distributed throughout the sample. Our results identify Sakharov oscillations as a generic hydrodynamic phenomenon of superfluids (*20*, *21*).

We perform the quench experiments in two-dimensional (2D) atomic superfluids. [For the details of the experimental setup, see (*22*).] We laser cool and Bose condense cesium atoms in an optical dipole trap, which is then adiabatically deformed into a highly oblate potential with a high harmonic vibrational frequency of $\omega_z = 2\pi \times$ 1900 Hz in the vertical (z) direction and a low frequency of $\omega_r = 2\pi \times 9$ Hz in the radial (r) direction. The atomic sample forms an almost pure 2D superfluid at an equilibrium temperature $T =$ 10 to 15 nK. The sample extends over 20 μm in the radial direction and, in the z direction, occupies the vibrational ground state with a harmonic oscillator length of $l_z = 200$ nm. The interaction strength of the 2D superfluid is characterized by a dimensionless parameter $g = \sqrt{8\pi}a/l_z$ (*23*), where the scattering length a is tunable via a magnetic Feshbach resonance (*19*).

To induce synchronous phonon excitations, we quench the interaction g from an initial value g_i to a final value g_f by switching the magnetic field. The switching time of the field is <300 μs, very fast compared to all relevant time scales in the radial direction. After the quench, we maintain the interaction at g_f for a variable hold time

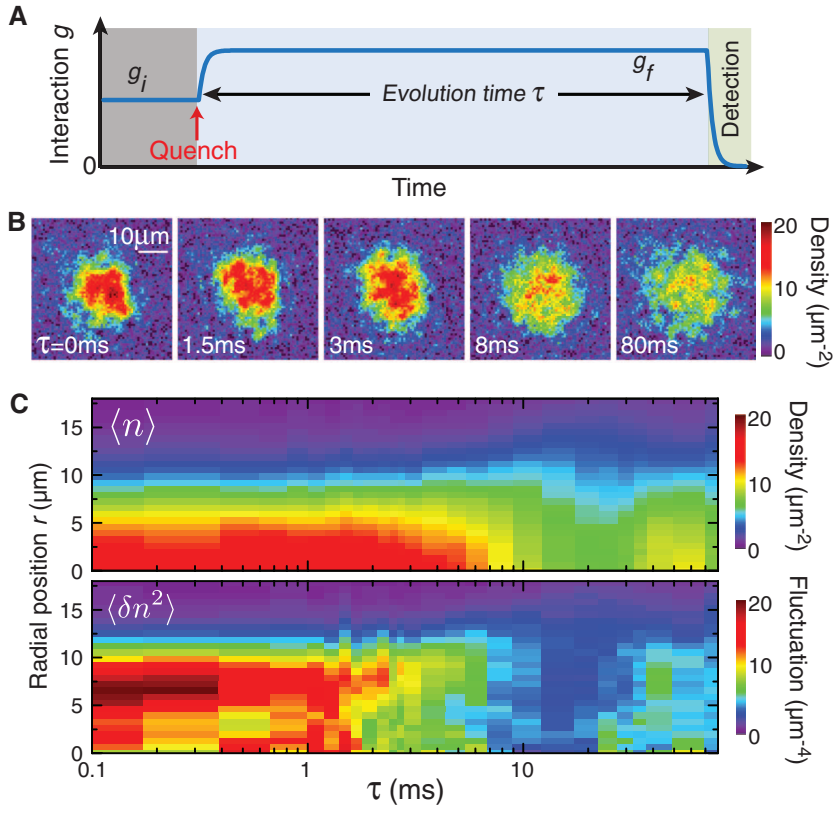


Fig. 1. Evolution of density and density fluctuations of atomic superfluids quenched to a stronger interaction. (**A**) Experimental procedure: The atomic interaction g is quenched from the value g_i to g_f for a time τ, and then the sample is imaged. (**B**) Single-shot images of the quenched sample ($g_i = 0.079$ to $g_f = 0.25$) after the indicated hold times. (**C**) Averaged radial density profile $\langle n(r)\rangle$ and density fluctuations $\langle \delta n^2(r)\rangle$ based on ~25 samples. Each sample contains ~5500 atoms.

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τ, and record the atomic density distribution in situ (*22*, *24*, *25*). The experimental procedure, images, and the averaged density profiles are shown in Fig. 1: After the interaction is quenched to a stronger value $g_f > g_i$, the sample expands and exhibits weak collective oscillations after ~50 ms, about half the radial trap period (Fig. 1C, upper panel). Density fluctuations $\langle \delta n^2 \rangle$ near the cloud center, by contrast, change drastically within the first few milliseconds (Fig. 1C, lower panel). This difference in time scale suggests a hydrodynamic behavior with fast local equilibration and a much slower global thermalization. After $\tau > 50$ ms, our observation on the density and fluctuation distributions is consistent with the sample evolving toward a new equilibrium described by the new interaction strength g_f (*22*, *24*).

To extract the dynamics of phonons and search for Sakharov oscillations, we calculate the structure factor of the quenched superfluids (*24*) $S(\mathbf{k},\tau) = \frac{\langle |\delta n(\mathbf{k},\tau)^2| \rangle}{N}$ in the first 8 ms. Here, $\delta n(\mathbf{k},\tau)$ is the Fourier transform of the density fluctuation $\delta n(\mathbf{r}, \tau)$ at hold time τ, $\mathbf{k}$ is the momentum wave vector, and N is the total particle number. The structure factor $S(\mathbf{k}, \tau)$ is analogous to the angular power spectrum used in analyzing the CMB radiation.

We evaluate the structure factor based on the central 32 × 32 pixels of the atomic images (pixel size: 0.44 μm^2), where the mean density n is almost uniform. Systematic fluctuations resulting from the photon shot-noise and imaging distortions have been removed (*24*). We then bin the spectrum azimuthally according to the wave number $k = |\mathbf{k}|$. Our extraction of $S(k)$ is limited to $k \leq 2$/μm by the imaging resolution and to $k > 0.3$/μm by the size of the sample.

In the time evolution of the density structure factor $S(k,\tau)$, we observe as many as four oscillations for $\tau \leq 8$ ms, and for quenches to both stronger and weaker interactions (Fig. 2). The exception is the smallest $k \leq 0.7$/μm, for which the oscillations may be overdamped. For $k \geq 0.7$/μm, the larger the k, the higher the oscillation frequency appears to be, and the smaller the amplitude. Comparing the quench-up and quench-down experiments, we see that the initial phases of the oscillations differ by π and that the oscillation periods are much shorter in the quench-up experiment at a similar wave number k. The latter can be qualitatively understood, as the sound speed for the quench-up experiments is expected to be higher than that in the quench-down experiments. A more quantitative discussion is given below.

We also observe Sakharov oscillations in the spatial density correlations (momentum domain). The density structure factor $S(k)$ evaluated at various hold times τ shows a nonmonotonic, oscillatory behavior in both quench-up and quench-down experiments (Fig. 3). The oscillations are particularly visible in the quench-down experiments. Starting with a superfluid with featureless correlations at $\tau = 0$, a peak grows near $k = 1$/μm at $\tau \sim 2$ ms and moves toward lower wave number as time evolves (Fig. 3B). At longer hold times

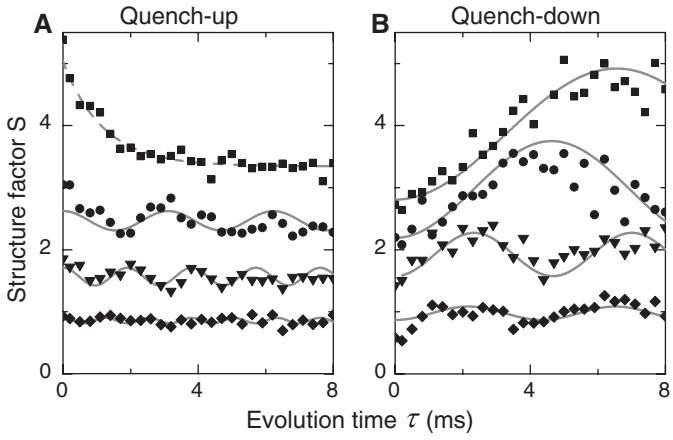


Fig. 2. Time evolution of density correlations in a quenched superfluid. (**A**) Quenches from $g_i = 0.079$ to $g_f = 0.14$: structure factors $S(k, \tau)$ measured at $k = 0.7$ (squares), 0.9 (circles), 1.3 (triangles), and 1.6 (diamonds)/μm are shown with a vertical offset of 0.5. Solid lines are fit to the data to determine the oscillation frequencies (see text). The dashed line is an exponential fit. (**B**) Quenches from $g_i = 0.25$ to $g_f = 0.079$: structure factors $S(k, \tau)$ at wave numbers $k = 0.7$ (squares), 0.8 (circles), 1.1 (triangles), and 1.3 (diamonds)/μm. Mean atomic density is $\bar{n} = 14$/μm^2 in (A) and 11/μm^2 in (B). Each sample contains ~5500 atoms within the central 32 × 32 pixels of the atomic images, and the total atom number is ~12,000.

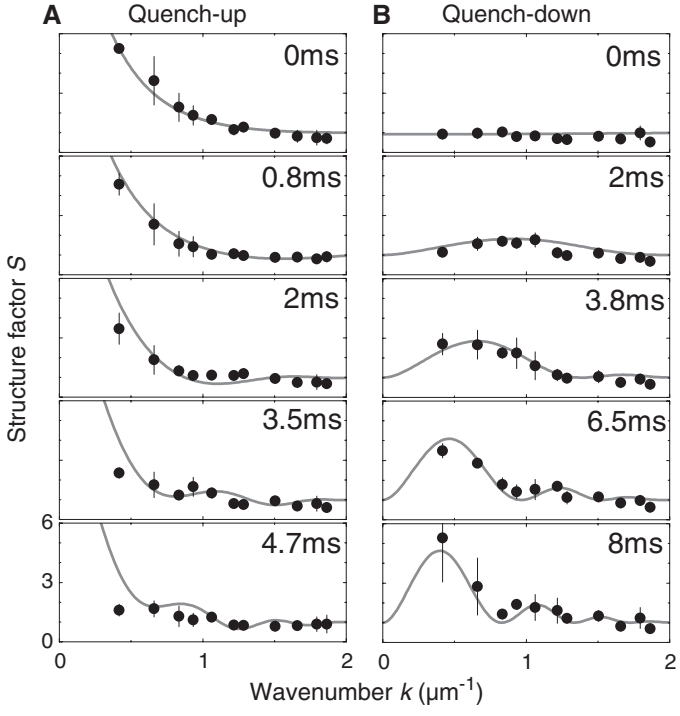


Fig. 3. Fourier spectrum of spatial density correlations in quenched superfluids. (**A**) The structure factors $S(k)$ (solid circles) are measured at different hold times τ after quenching the interaction from $g_i = 0.079$ to $g_f = 0.14$. For quench-down experiments (**B**) with $g_i = 0.25$ and $g_f = 0.079$, Sakharov oscillations manifest as the multiple-peak structure appearing after 6.5 ms. For quench-up measurements (A), oscillations are less distinct. Sample parameters are the same as in Fig. 2. Solid lines are based on fits to the experiment shown in Fig. 2 (see text). All panels have the same scales for both x and y axes. Error bars show the SDs of the measurement.

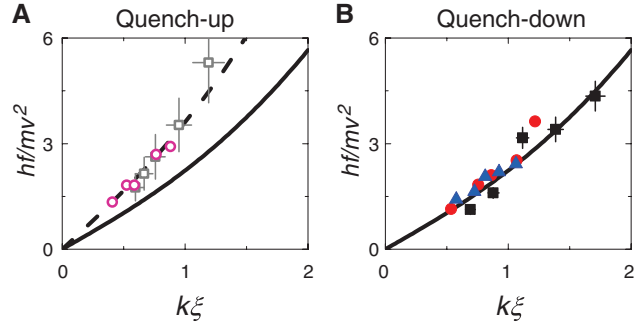


Fig. 4. Sakharov oscillation frequencies and energy dispersion. In (**A**), samples are prepared at $\bar{n} = 13.5$/μm^2 and $g_i = 0.079$, and are quenched to $g_f = 0.14$ (open squares) and 0.19 (open circles). In (**B**), samples are prepared at $\bar{n} = 12$/μm^2 and $g_i = 0.25$, and are quenched to $g_f = 0.079$ (squares), 0.1 (triangles), and 0.13 (circles). Solid lines are theory predictions based on the Bogoliubov dispersion $hf/mv^2 = 2k\xi\sqrt{1 + k^2\xi^2/4}$. Dashed line is an empirical fit that scales up the Bogoliubov result by a factor of 1.65. Error bars of the measurement are dominated by systematic uncertainties.

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$\tau > 5$ ms, a second peak emerges within our detectable range near $1/\mu m < k < 1.5/\mu m$. The signal-to-noise ratios for the peaks are statistically limited to 1 to 2 for images taken at a fixed hold time. Combining data points at all times, one recovers clear oscillations as observed in Fig. 2B. The multiple peaks and troughs in momentum space result from the interference of sound waves with different wavelengths and are the key features of Sakharov oscillations in the angular spectrum of the CMB radiation. Moreover, moving acoustic peaks as time evolves suggests that the correlations are spreading out at a finite speed of sound. For the quench-up experiments, the oscillations are less clear, owing to the limited imaging resolution and the sample size. Nonetheless, we clearly observe that correlations are suppressed at smaller k as time evolves. Spreading of correlations along the acoustic "light-cone" was also reported in a quenched atomic Mott insulator (*26*).

The oscillations in the time and space domains can be understood as the interference of counter-propagating phonon pairs $\hat{b}^{\dagger}_{\pm k} e^{\pm ikr - i\epsilon(k)\tau/\hbar}$, where $\hat{b}^{\dagger}_{\pm k}$ is the creation operator of phonons with momentum $\pm k$ and energy $\epsilon(k)$. Assuming that phonons are long-lived, the structure factor follows a simple form (*10*, *20*), $S(k,\tau) = S(k,0) + 2B_k \cos\phi \sin^2(\pi f\tau)$, where $B_k > 0$ is the oscillation amplitude, the oscillation frequency is given by $f(k) = 2\epsilon(k)/h$, and the relative phase is $\phi = 0$ for quench-up experiments and $\phi = \pi$ for quench-downs (*20*). Adopting sinusoidal fits to the measured data in Fig. 2, we determine the oscillation frequencies for various k and g_f. The result in turn provides good fits to the data shown in Fig. 3 (*20*).

We summarize five sets of measurements on quenched superfluids and compare the oscillation frequencies to the predictions from the Bogoliubov theory: $\epsilon(k) = v\hbar k\sqrt{1+k^2\xi^2/4}$, where $v = \hbar\sqrt{\overline{n}g_f}/m$ is the speed of sound and $\xi = \hbar/mv$ is the healing length. Plotting the frequencies in the dimensionless units based on calculated v and ξ, the data in all three quench-down measurements collapse to a single curve, which agrees with the Bogoliubov theory (Fig. 4B). Quench-up experiments, however, show consistently 65% higher frequencies than the prediction (Fig. 4A). The discrepancy likely results from the effects of strong initial density fluctuations in quench-up experiments and finite temperature (*20*).

The space-time dependence of the density correlations in quenched superfluids not only supports the picture of Sakharov acoustic oscillations, but also suggests that Sakharov oscillation is a universal feature of a quenched hydrodynamic system far from thermal equilibrium. The time and spatial scales of the oscillations are related by the speed of sound v, and the observed propagation of Sakharov acoustic peaks is consistent with the sonic horizon $k = \pi/v\tau$ within which the waves can interfere. In particular, good agreement with the Bogoliubov theory is found when the interaction is quenched to smaller values, and the growing multipeak structure in the density noise power spectrum resembles that in the CMB radiation spectrum. The observation of Sakharov oscillations in a quenched atomic superfluid raises prospects of investigating universal hydrodynamic phenomena in a laboratory setting, as well as of extending the current experimental tools to address exciting topics in cosmology and gravitational physics such as Hawking radiation (*13*) or Unruh effect (*27*).

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Supplementary Materials

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Materials and Methods
References (*28*–*30*)

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An Atomic Clock with 10^{-18} Instability

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Atomic clocks have been instrumental in science and technology, leading to innovations such as global positioning, advanced communications, and tests of fundamental constant variation. Timekeeping precision at 1 part in 10^{18} enables new timing applications in relativistic geodesy, enhanced Earth- and space-based navigation and telescopy, and new tests of physics beyond the standard model. Here, we describe the development and operation of two optical lattice clocks, both using spin-polarized, ultracold atomic ytterbium. A measurement comparing these systems demonstrates an unprecedented atomic clock instability of 1.6×10^{-18} after only 7 hours of averaging.

Quantum mechanical absorbers such as atoms serve as the best available time and frequency references: They are isolatable, possess well-defined transition frequencies, and exist in abundant identical copies. With more than 50 years of development, clocks based on microwave oscillators referenced to atomic transitions now define the Système International (SI) second and play central roles in network synchronization, global positioning systems, and tests of fundamental physics (*1*, *2*). Under development worldwide, optical clocks oscillate 10^5 times faster than their microwave predecessors, dividing time into finer intervals (*3*). Although microwave clocks such as the Cs fountain have demonstrated time and frequency measurements of a few parts in 10^{16} (*4*, *5*), optical clocks now measure with a precision of 1 part in 10^{17} (*6*–*9*).

A clock's instability specifies how its ticking fluctuates over time, a characteristic generally quantified by the Allan deviation (*10*). No time or frequency standard can make measurements

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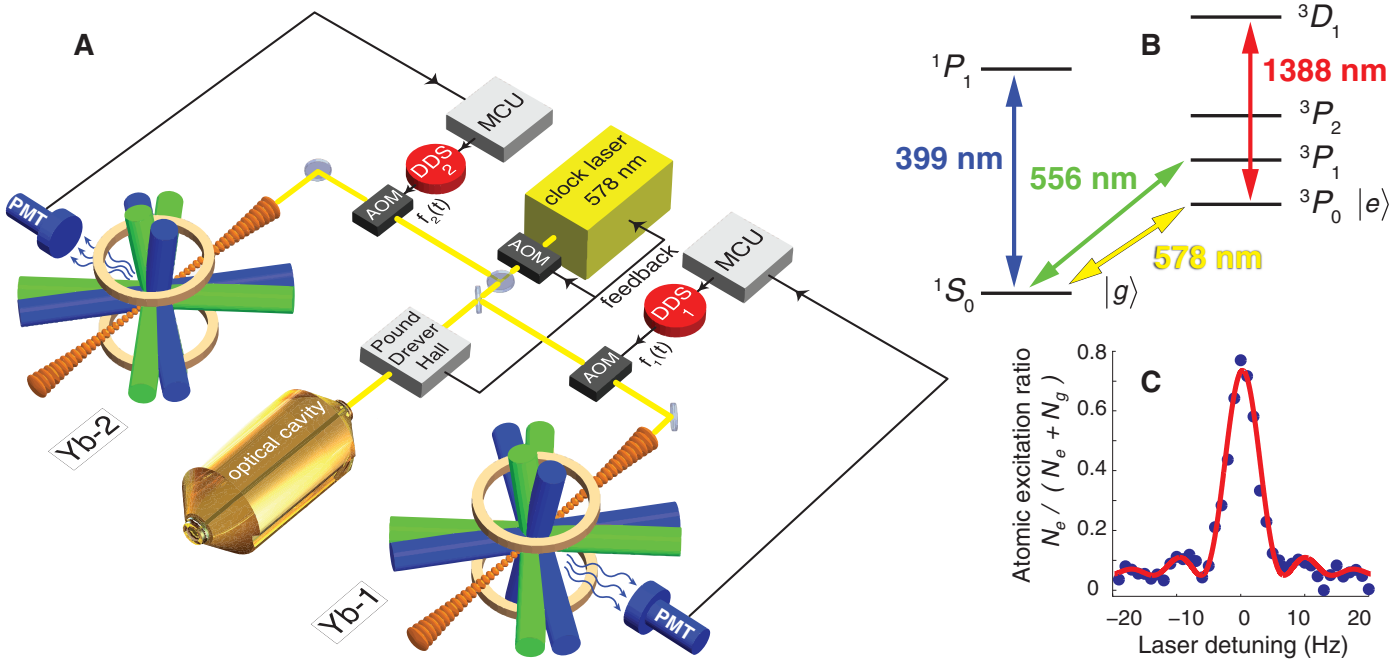


Fig. 1. Experimental realization of the Yb optical lattice clocks. (A) Laser light at 578 nm is prestabilized to an isolated, high-finesse optical cavity using Pound-Drever-Hall detection and electronic feedback to an AOM and laser piezoelectric transducer. Fibers deliver stabilized laser light to the Yb-1 and Yb-2 systems. Resonance with the atomic transition is detected by observing atomic fluorescence collected onto a PMT. The fluorescence signal is digitized and processed by a microcontroller unit (MCU), which computes a correction frequency, $f_{1,2}(t)$. This correction frequency is applied to the relevant AOM by way of a direct digital synthesizer (DDS) and locks the laser frequency onto resonance with the clock transition. **(B)** Relevant Yb atomic energy levels and transitions, including laser-cooling transitions (399 and 556 nm), the clock transition (578 nm), and the optical-pumping transition used for excited-state detection (1388 nm). **(C)** A single-scan, normalized excitation spectrum of the $^1S_0$-$^3P_0$ clock transition in ^{171}Yb with 140-ms Rabi spectroscopy time; the red line is a free-parameter sinc^2 function fit.

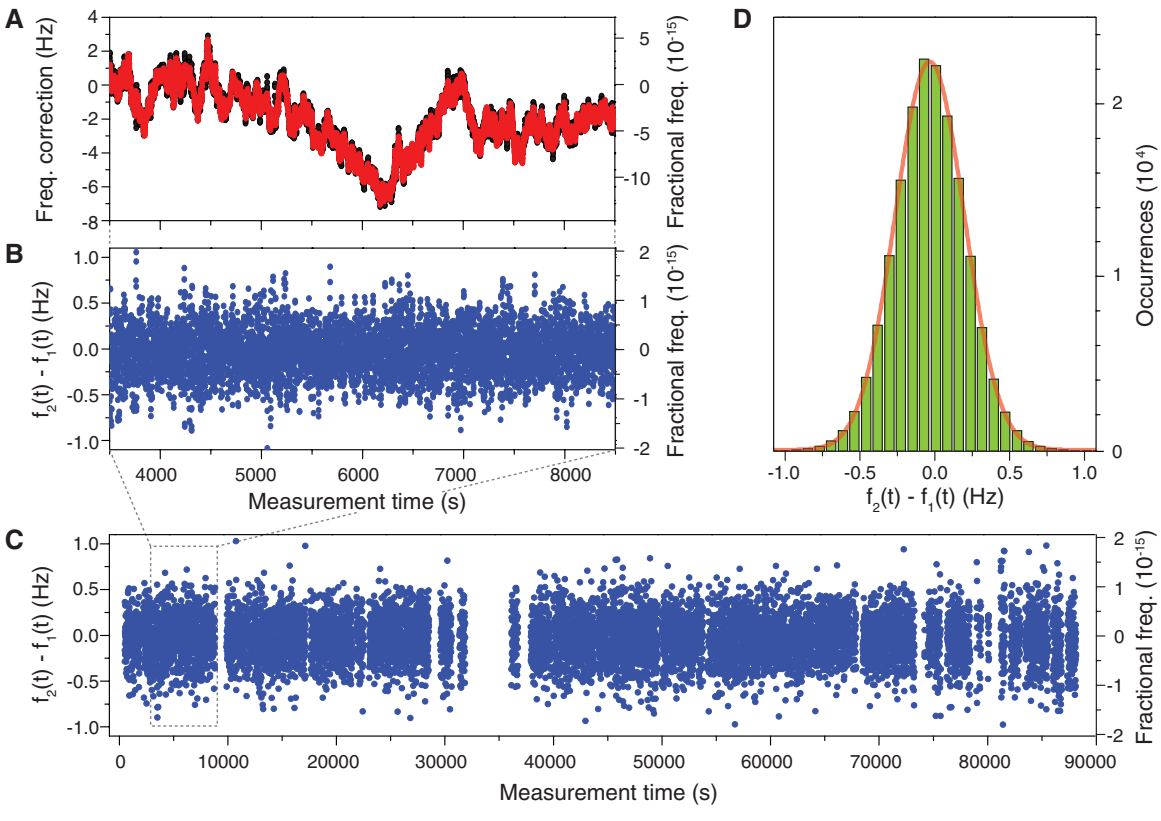


Fig. 2. Frequency comparison between the Yb optical lattice clocks. (A) Correction frequencies, $f_{1,2}(t)$, are shown in red and black. Dominant LO fluctuations are due to the cavity and are, thus, common to the atomic systems. **(B)** Frequency difference, $f_2(t) - f_1(t)$, between the two Yb clock systems for a 5000-s interval. **(C)** Data set $f_2(t) - f_1(t)$ over a 90,000-s interval. Gaps represent data rejected before data analysis due to servo unlocks. **(D)** Histogram of all data and a Gaussian fit ($\chi^2_r = 0.9996$).

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better than the statistical precision set by its instability. Further, a clock's systematic uncertainty is often constrained by its long-term instability. For these reasons, and because many timing applications require only exquisite instability, the instability represents perhaps the most important property of an atomic standard.

In pursuit of lower instability, an optical lattice clock uses a stabilized laser referenced to many (10^3 to 10^6) alkaline earth (or similar) atoms confined in an optical standing wave. Alignment of the clock interrogation laser along the direction of tight lattice confinement eliminates most Doppler and motional effects while probing the ultranarrow-band electronic clock transition. These atoms are interrogated simultaneously, improving the atomic detection signal-to-noise ratio and, thus, instability, which is limited fundamentally by quantum projection noise (QPN) (*11*). Like other cycled atomic clocks, the lattice clock suffers from a technical noise source known as the Dick effect, arising when an oscillator's noise is periodically sampled (*12*, *13*). Cavity-stabilized lasers with low thermal noise have reduced the Dick effect, enabling clock instability below 10^{-15} at short times (*14*). Recently, an uncorrelated comparison of two strontium lattice clocks revealed clock instability of 3×10^{-16} at short times, averaging to 1×10^{-17} in 1000 s (*8*) or, in another case, reaching the 10^{-17} level in 20,000 s (*9*). Here, by comparing two independent optical lattice clocks using ultracold ^{171}Yb, we demonstrate a clock instability of 1.6×10^{-18} in 25,000 s.

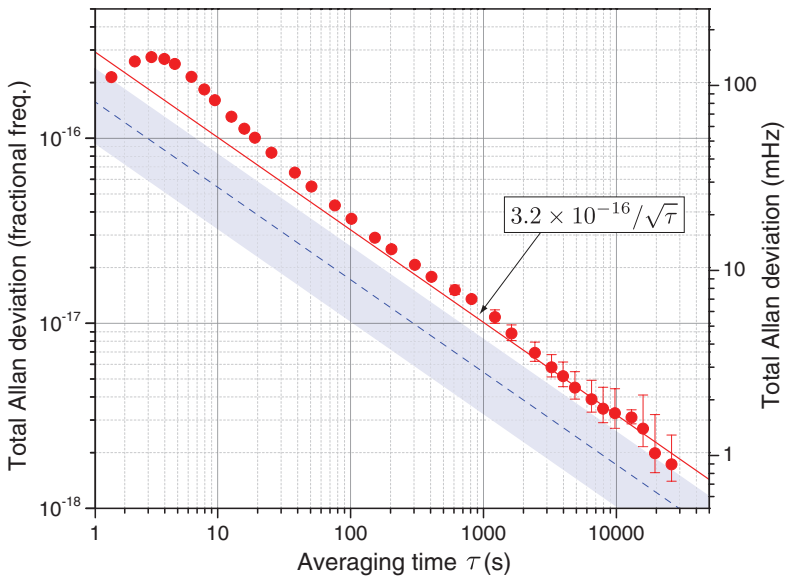


Fig. 3. Measured instability of a Yb optical lattice clock. Total Allan deviation of a single Yb clock, $[f_2(t) - f_1(t)]/\sqrt{2}$ (red circles), and its white-frequency-noise asymptote of $3.2 \times 10^{-16}/\sqrt{\tau}$ (red solid line). The blue dashed line represents the estimated combined instability contributions from the Dick effect ($1.4 \times 10^{-16}/\sqrt{\tau}$) and QPN ($1 \times 10^{-16}/\sqrt{\tau}$); the shaded region denotes uncertainty in these estimates. Error bars indicate 1σ confidence intervals.

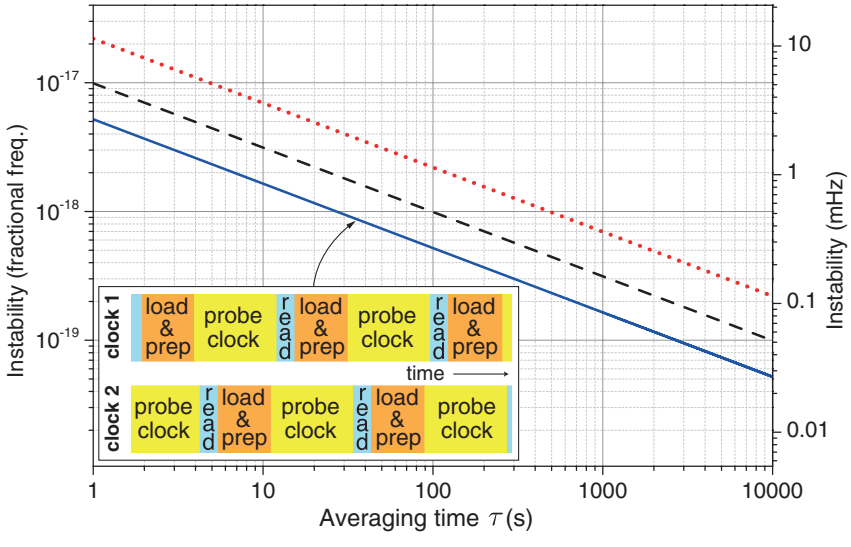


Fig. 4. Calculated instability limits toward the goal of 1×10^{-18} in 100 s. The Dick limit (red dotted line) is reduced by using a hypothetical LO four times as stable as the LO used in our experiment. The QPN limit is shown under the same conditions (black dashed line), assuming 50,000 atoms. The inset illustrates an interleaved interrogation of two atomic systems, allowing continuous monitoring of the LO for suppression of the Dick effect. Dead times from atomic preparation or readout in one system are synchronized with clock interrogation in the second system. The solid blue line indicates the suppressed Dick instability in the interleaved interrogation scheme using Ramsey spectroscopy with an unimproved LO.

Both clock systems, referred to here as Yb-1 and Yb-2, independently cool and collect ^{171}Yb atoms from thermal beams into magneto-optical traps [see Fig. 1 and (*15*)]. Two stages of laser cooling, first on the strong $^1S_0$-$^1P_1$ cycling transition at 399 nm, followed by the weaker $^1S_0$-$^3P_1$ intercombination transition at 556 nm, reduce the atomic temperature from 800 K to 10 μK. Each cold atom sample is then loaded into an optical lattice with ~300E_r trap depth (E_r/k_B = 100 nK; E_r, recoil energy; k_B, Boltzmann's constant) formed by retroreflecting ~600 mW of laser power, fixed at the "magic" wavelength $\lambda_m \approx 759$ nm (*16*) by a reference cavity. At λ_m, both electronic states of the clock transition are Stark-shifted equally (*17*, *18*). For the measurements described here, ~5000 atoms captured by each lattice are then optically pumped to one of the two ground-state spin projections $m_F = \pm 1/2$ using the $^1S_0$-$^3P_1$ transition. After this state preparation, applying a 140-ms-long π pulse of 578-nm light resonant with the $^1S_0$-$^3P_0$ clock transition yields the spectroscopic line shape shown in Fig. 1C, with a Fourier-limited linewidth of 6 Hz. Experimental clock cycles alternately interrogate both m_F spin states canceling first-order Zeeman and vector Stark shifts. The optical local oscillator (LO) is an ultrastable laser servo-locked to a high-finesse optical cavity (*14*) and is shared by both Yb systems. Light is frequency-shifted into resonance with the clock transition of each atomic system by independent acousto-optic modulators (AOMs). Resonance is detected by monitoring the $^1S_0$ ground-state population (N_g) and $^3P_0$ excited-state population (N_e). A laser cycles ground-state atoms on the $^1S_0$-$^1P_1$ transition while a photomultiplier tube (PMT) collects the fluorescence, giving a measure of N_g. After 5 to 10 ms of cycling, these atoms are laser-heated out of the lattice. At this point, N_e is optically pumped to the lowest-lying $^3D_1$ state, which decays back to the ground state. The $^1S_0$-$^1P_1$ transition is cycled again, now measuring N_e. Combining these measurements yields a normalized mean excitation $N_e/(N_e + N_g)$. During spectroscopy, special attention was paid to

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eliminating residual Stark shifts stemming from amplified spontaneous emission of the lattice lasers, eliminating residual Doppler effects from mechanical vibrations of the apparatus correlated with the experimental cycle, and controlling the cold collision shift due to atomic interactions within the lattice (*19*).

By measuring the normalized excitation while modulating the clock laser frequency by ±3 Hz, an error signal is computed for each Yb system. Subsequently, independent microprocessors provide a digital frequency correction $f_{1,2}(t)$ at time t to their respective AOMs, thereby maintaining resonance on the line center. In this way, though derived from the same LO, the individual laser frequencies for Yb-1 and Yb-2 are decoupled and are instead determined by their respective atomic samples (for all but the shortest time scales). The frequency correction signals $f_{1,2}(t)$ are shown in Fig. 2A for a 5000-s interval. Because the experimental cycles for each clock system are unsynchronized and have different durations, $f_{1,2}(t)$ signals are interpolated to a common time base and subtracted to compute the frequency difference between Yb-1 and Yb-2, as shown in Fig. 2, B to D. Measurements such as these were repeated several times for intervals of ~15,000 s, demonstrating a clock instability reaching 4×10^{-18} at 7500 s. While collecting data over a 90,000-s interval, we observed the instability curve in Fig. 3, shown as the total Allan deviation for a single Yb clock. Before data analysis, ~25% of the attempted measurement time was excluded due to laser unlocks and auxiliary servo failures (*15*). Each clock servo had an attack time of a few seconds, evidenced by the instability bump near 3 s. At averaging times $\tau = 1$ to 5 s, the instability is comparable to previous measurements (*14*) of the free-running laser system, and at long times, the instability averages down like white frequency noise as $\sim 3.2 \times 10^{-16}/\sqrt{\tau}$ (for τ in seconds), reaching 1.6×10^{-18} at 25,000 s.

Also shown in Fig. 3 is an estimate of the combined instability contribution (blue dashed line) from the Dick effect and QPN (shaded region denotes the uncertainty of the estimate). These contributions must be reduced if 10^{-18} instability is desired at time scales under 100 s. Substantial reductions of QPN are possible with the use of higher atom numbers and longer interrogation times. Further stabilization of the optical LO will continue to reduce the Dick effect, by both lowering the laser frequency noise down-converted in the Dick process and allowing increased spectroscopy times for higher duty cycles. Improved LOs will use optical cavities exhibiting reduced Brownian thermal-mechanical noise by exploiting cryogenic operation (*20*), crystalline optical coatings (*21*), longer cavities, or other techniques (*14*). Figure 4 demonstrates the advantage of improving the present LO, with four times less laser frequency noise and four times longer interrogation time (corresponding to a short-term laser instability of $\sim 5 \times 10^{-17}$). The red dotted line gives the Dick instability, whereas the black dashed line indicates the QPN limit, assuming a moderate 50,000 atom number.

Noting that the calculated Dick effect remains several times higher than the QPN limit, we consider an alternative idea first proposed for microwave ion clocks: interleaved interrogation of two atomic systems (*13*). By monitoring the LO laser frequency at all times with interleaved atomic systems, the aliasing problem at the heart of the Dick effect can be highly suppressed. The solid blue line in Fig. 4 illustrates the potential of a simple interleaved clock interrogation using Ramsey spectroscopy. Even with the present LO, the Dick effect is decreased well below the QPN limit afforded by a much-improved LO (black dashed line). In this case, spin squeezing of the atomic sample could reduce the final instability beyond the standard quantum limit set by QPN (*22*). The two-system, interleaved technique requires spectroscopy times that last one half or more of the total experimental cycle. By extending the Yb clock Ramsey spectroscopy time to >250 ms, we achieved a 50% duty cycle for each system, demonstrating the feasibility of this technique. Further suppression of the Dick effect can be achieved with the use of a more selective interleaving scheme. Duty cycles ≥50% can also be realized with the aid of nondestructive state detection (*23*).

Another important property of a clock is its accuracy, which results from uncertainty in systematic effects that alter a standard's periodicity from its natural, unperturbed state. In 2009, we completed a systematic analysis of Yb-1 at the 3×10^{-16} uncertainty level (*16*). Since then, we reduced the dominant uncertainty due to the blackbody Stark effect by one order of magnitude (*24*). With its recent construction, Yb-2 has not yet been systematically evaluated. The fact that the instability reaches the 10^{-18} level indicates that key systematic effects (e.g., the blackbody Stark effect, atomic collisions, lattice light shifts) on each system are well controlled over the relevant time scales. The mean frequency difference in Fig. 2 was $\langle f_2(t) - f_1(t) \rangle = -30$ mHz, which is within the Yb-1 uncertainty at 10^{-16}. Systematic effects on each system can now be efficiently characterized beyond the 10^{-17} level. With continued progress, we envision 10^{-18} instability in only 100 s and long-term instability well below 10^{-18}.

Clock measurement at the 10^{-18} level can be used to resolve spatial and temporal fluctuations equivalent to 1 cm of elevation in Earth's gravitational field (*25*–*28*), offering a new tool for geodesy, hydrology, geology, and climate change studies. Space-based implementations can probe alternative gravitational theories, e.g., by measuring red-shift deviations from general relativity with a precision that is three orders of magnitude higher than the present level (*28*). Though present-day temporal and spatial variation of fundamental constants is known to be small (*6*, *29*, *30*), 10^{-18}-level clock measurements can offer tighter constraints. Finally, timekeeping improvements can benefit navigation systems, telescope array synchronization (e.g., very-long-baseline interferometry), secure communication, and interferometry and can possibly lead to a redefinition of the SI second (*9*).

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Supplementary Materials

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Supplementary Text
Table S1

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Reversibly Assembled Cellular Composite Materials

Kenneth C. Cheung* and Neil Gershenfeld

We introduce composite materials made by reversibly assembling a three-dimensional lattice of mass-produced carbon fiber–reinforced polymer composite parts with integrated mechanical interlocking connections. The resulting cellular composite materials can respond as an elastic solid with an extremely large measured modulus for an ultralight material (12.3 megapascals at a density of 7.2 milligrams per cubic centimeter). These materials offer a hierarchical decomposition in modeling, with bulk properties that can be predicted from component measurements and deformation modes that can be determined by the placement of part types. Because site locations are locally constrained, structures can be produced in a relative assembly process that merges desirable features of fiber composites, cellular materials, and additive manufacturing.

Carbon-fiber–reinforced composite materials can improve efficiency in engineered systems (for example, airframes) by reducing structural weight for given strength and stiffness requirements (*1*), but challenges with manufacturing and certification have slowed their adoption. High-performance composite components are conventionally constructed with many continuous fibers that span the shape of a component and are embedded in a resin matrix that is either pre-impregnated or subsequently infused (*2*). Parts produced in this way typically require custom tooling to form them, pressurization for consolidation, and heat for matrix curing. Each of these processes multiplies the time, cost, and inflexibility of design, production, and certification. Joint systems between different parts add further complexity and structural vulnerabilities (*2*).

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The approach that we developed uses many small identical parts as regular building blocks. The parts integrate unidirectional fiber composite beams and looped fiber load-bearing holes that are reversibly linked, like chains, to form volume-filling lattice structures. These parts can be mass-produced and then assembled to fill arbitrary structural shapes, with a resolution prescribed by the part scale, which is chosen to match the variability of the boundary stress encountered in an application. Each type of identical part can be individually qualified, and as a cellular material, the periodic nature of their assemblies simplifies the analysis and prediction of their behavior.

Fiber composites have been used to construct truss cores (*3*, *4*) and structural frames (*5*, *6*), with bonded assembly of substructures or continuous winding of fibers over a structure. Examples of such truss cores have been reported with continuous two-dimensional (2D) geometric symmetry and nearly ideal but highly anisotropic specific modulus scaling (*4*). Three-dimensional (3D) open-cell lattice materials occur in natural and engineered systems (*7*, *8*), spanning many length scales (*9*, *10*), with mechanical properties that scale with relative density according to the geometry of the cellular structure (*7*). Their response is characterized as displaying either stretch-dominated or transverse beam bending–dominated microstructural behavior, based on periodic mechanical models (*7*, *11*). For the Young's modulus E, ideal stretch-dominated scaling with density ρ follows a proportional law, $E \propto \rho$ (*12*); common stochastic foams follow a quadratic law, $E \propto \rho^2$ (*7*), associated with transverse beam bending–dominated behavior; and at ultralight densities, a further reduced cubic scaling law, $E \propto \rho^3$, is commonly observed, such as with aerogels and aerogel composites (*7*, *11*, *13*, *14*).

The dependence of this scaling performance on geometry is seen in nonstochastic lattice-based materials that have nearly ideal $E \propto \rho$ scaling, with high coordination numbers (node connectedness) relative to stochastic foams (*15*, *16*). These structures have been implemented thus far only in relatively dense engineered materials. For the ultralight regime [below 10 mg/cm^3 (*7*)], the $E \propto \rho^2$ scaling seen in denser stochastic cellular materials has recently been reported for electroplated tubular nickel microlattices (*17*), as well as carbon-based open-cell stochastic foams, including carbon microtube aerographite (*18*), and graphene cork (*19*). Reversibly assembled cellular composites extend stretch-dominated lattice-based materials to the ultralight regime, with 3D symmetry derived from the linked geometry. The high-performance characteristics of these new materials depend on the framework rigidity of the nonstochastic lattice geometry with high coordination number, the slenderness that can be achieved in buckling-limited fiber composite strut members, and the scaling of the density cost of reversible mechanical connections.

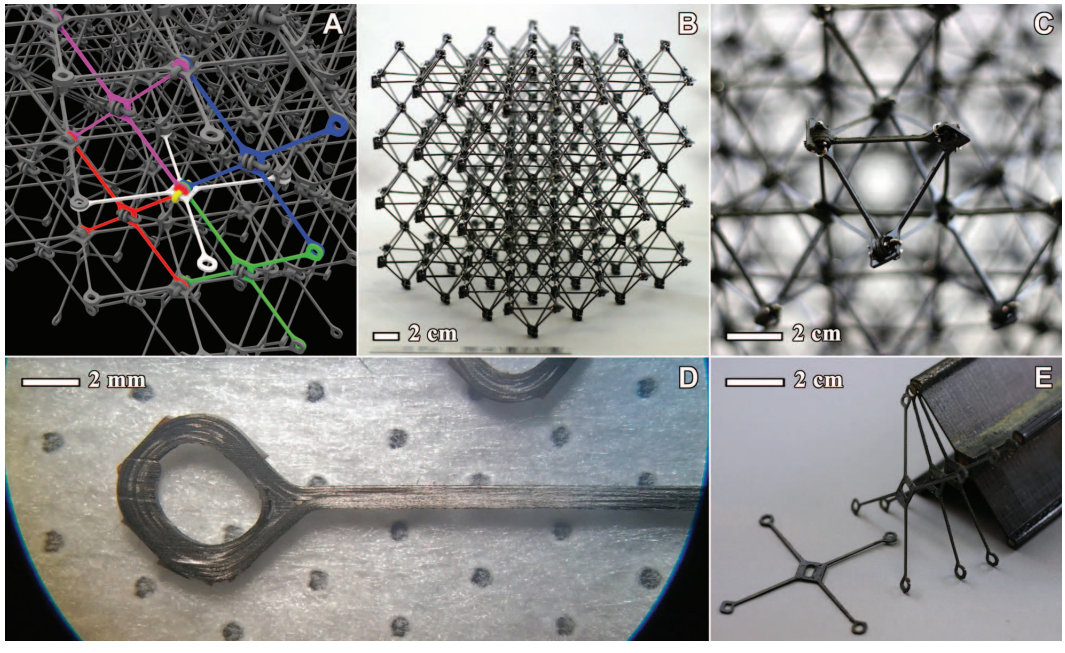


Fig. 1. Structural components. (**A**) Assembly of a "cuboct" lattice of vertex-connected octahedrons from planar components linked by shear clips [see fig. S5 (*20*) for additional detail of the spatial arrangement of parts]. (**B**) Carbon fiber–reinforced polymer composite cuboct lattice. (**C**) Reversible joints of components in the cuboct lattice. (**D**) Micrograph showing fiber orientation around connection holes and along strut members. (**E**) Slicing components from wound/oriented-fiber stock rather than conventionally cutting quasi-isotropic laminate.

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We designed the connections to be stiffer and stronger than the strut members, so that the response of these structures is governed by the struts [see supplementary materials (*20*)]. Dimensional scaling methods (*7*), extended to include the connections (*20*), show that the mass density cost of such robust connections—which scale with the cross-sectional area of strut members—is low for ultralight materials, where strut member slenderness dominates mass density scaling. We define the relative density (ρ/ρ_s) of these materials as the sum of the relative density contribution of the strut members (ρ_m/ρ_s) and the relative density contribution of the connections (ρ_c/ρ_s). The strut members have a thickness t and length l. The connections were designed to transfer forces through load-bearing surface contacts, and this constraint required that the characteristic dimensions of the connections must scale with the cross-sectional area of the attached strut members, t^2, because this dimension determines the maximum possible stress transferrable through the joint.

These definitions give a cubic scaling relation between the relative mass contribution of the joints and the thickness-to-length ratio of the strut members [$\rho_c/\rho_s \propto C_c(t/l)^3$, where C_c is the connection contribution constant determined by the lattice geometry]. We find that the relative density contribution of the strut members is governed by quadratic scaling with the thickness-to-length ratio of the strut members [$\rho_m/\rho_s \propto C_m (t/l)^2$], which agrees with the literature on classical cellular materials (*7*, *11*). Mechanical properties (such as modulus and strength) scale with overall relative density (*7*), which in turn scales primarily with the strut and not the connection, because we consider only open-cell lattices with slender strut members [$t/l < 0.1$ (*7*)], and because the geometric constants C_c and C_m are of the same order of magnitude [$\rho/\rho_s \propto C_c (t/l)^3 + C_m (t/l)^2$; see supplementary materials for expanded derivation and tables for geometric constants (*20*)]. The density cost of the mechanical joints decreases with increasing strut member slenderness (decreasing t/l) and decreasing relative density.

The lattice geometry that we introduce here is a "cuboct" cubic lattice of vertex-connected octahedrons, similar to the perovskite mineral structure. It was chosen as a minimally spatially dense lattice with a regular polyhedral unit cell that satisfies Maxwell's rigidity criterion (*21*), and has a coordination number z of eight. Comparing lattice geometries, the dependence of the relative density on the coordination number is small relative to the dependence on the strut member slenderness (*7*), even when including the contribution of connections. As shown in Fig. 1, the reinforcing fibers were wound around the connection holes to optimize their load-bearing capacity while coupling them to strut members, which themselves retain uniaxial fiber orientation. The cross-shaped parts tiled space to form the cuboct lattice structure with each part contributing four conjoined strut members to one locally central node and one strut member to four peripheral nodes in the lattice. After all parts at each connection were in place, a shear clip was inserted through the four coincident connection holes (Fig. 1A).

The assembled material responded as an elastic solid in both tension and compression, with a linear regime followed by a nonlinear superelastic deformation mode (Fig. 2A). The residual hysteresis was primarily caused by the fixture [fig. S1 (*20*)]. The modulus data in Fig. 3 were calculated from the linear elastic regime [table S1 (*20*)], and for comparison the in-plane properties of 2D stock laminate were used as an upper-bound estimate of the modulus of the ideal 3D constituent solid material (*7*). Shown in fig. S2 is the same cuboct lattice geometry 3D-printed in acrylic at varying densities, with corresponding modulus measurements shown in Fig. 3. Existing ultralight materials are shown for comparison; observed reductions from ideal scaling (*7*) have been explained by geometries that are poorly modeled

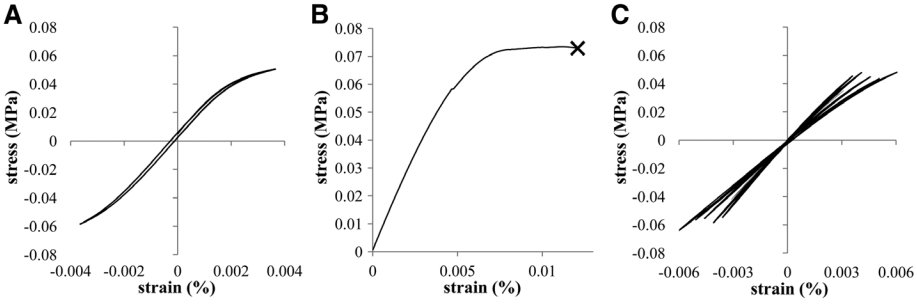


Fig. 2. Mechanical response. (**A**) Load cycling under compression and tension, showing a linear elastic response followed by a nonlinear superelastic response due to coordinated buckling [image and simulation shown in fig. S1 (*20*)]. (**B**) Testing to failure, defined by an abrupt decrease in stress by at least 10%, with failure by microstructural beam bending failures and associated $\sigma_{max} \propto \rho^{1.5}$ scaling (*7*). (**C**) Elastic load cycling after failure, showing incremental softening.

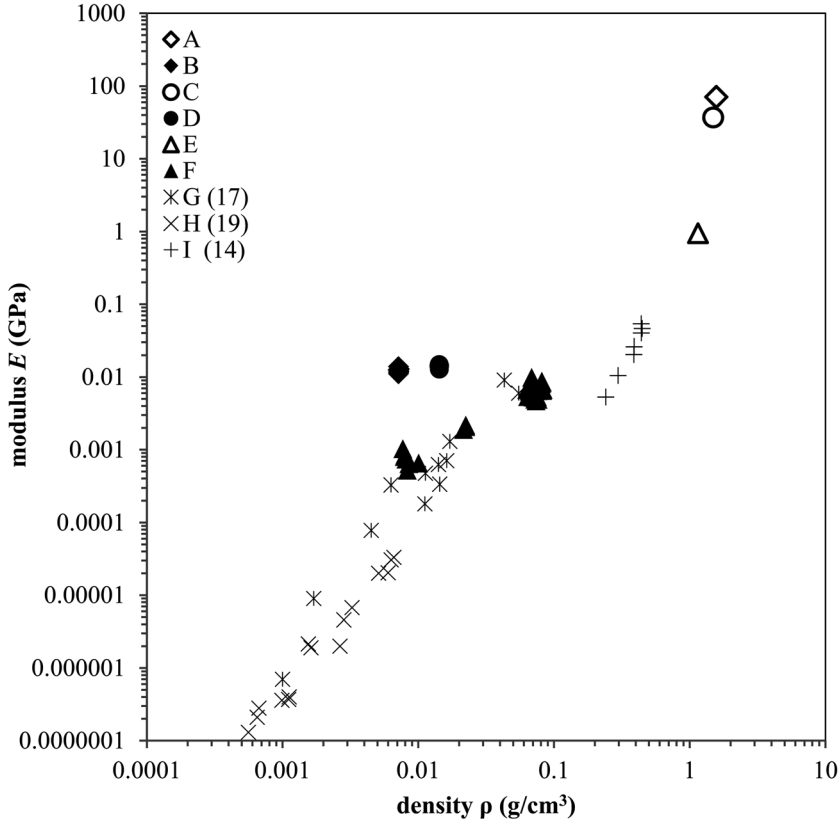


Fig. 3. Materials comparison. Young's modulus versus density for (A) unidirectional carbon fiber–reinforced polymer composite solid (along fiber axis), (B) reversibly assembled cellular composite material with wound/oriented-fiber parts, (C) conventional quasi-isotropic carbon fiber–reinforced polymer composite solid (laminate measured along quasi-isotropic plane), (D) reversibly assembled cellular composite material with parts conventionally cut from quasi-isotropic laminate, (E) acrylic solid, (F) acrylic cuboct lattice-based cellular material, (G) metallic micro-lattice (*17*), (H) graphene cork (*19*), and (I) silica aerogel composite (*14*). Data tables are provided in the supplementary materials (*20*).

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by the simple periodic models (*22*), and by natural distributions of morphological defects (*23*).

The modulus of the reversibly assembled cellular composite structure was more than an order of magnitude greater than that of reported ultralight materials, 12.3 MPa at a density of 7.2 mg/cm^3. We attribute the nonlinear elastic behavior to a multi-axial elastic instability of the lattice, a complex coordinated elastic buckling of the strut members. The resulting geometry is similar to a Jahn-Teller distortion of an octahedral complex with respect to orientation about the octahedral centers. Elastic folding or pleating across a lattice structure has been described as a coordinated antisymmetric twisting stress response in 2D lattices (*24*), and plastic deformations have been seen in auxetic lattice materials (*7*). We observed similar responses in three dimensions [see movie S1, showing corresponding affine rotations of terminal end nodes during loading (*20*)].

Figure 2B shows the plateau before failure, as defined by an abrupt decrease in stress by at least 10%. In Fig. 2C, repeated cycling in the elastic limit is shown after failure events. Unlike conventional composites, which fail catastrophically, these structures can fail incrementally because of the nonlinear deformation phase and the multiplicity of joints and links. These results are supported by finite-element simulations (ANSYS software) with finely meshed rigid body models. In addition to convergence to the observed coordinated buckling mode [fig. S3 (*20*)], these simulations also accurately predict the relative strength scaling observed in load test experiments. These results are consistent with the observation that open-cell lattice materials fail through microstructural bending failures in strut members, with $\sigma_{max} \propto \rho^{1.5}$ (*7*). The simulations also suggest that the coordinated buckling phenomenon, as well as the modulus measurements, is not dominated by edge effects (*25*), with minimal influence on overall results beyond characteristic dimensions exceeding several units [fig. S4 (*20*)].

The ability to tune anisotropic mechanical properties of fiber composite materials is considered to be an important capability (*26*). The discrete construction of reversibly assembled cellular composites introduces a new design degree of freedom that allows global functional properties to be determined by the local placement of compatible heterogeneous components. Figure 4 shows three structures with the same lattice geometry, differing only in the relative locations of a more-rigid and less-rigid component, which under identical constraints and loading will axially compress or buckle with prescribed modes. In this fashion, heterogeneous elements can be incorporated into multifunctional structures with properties determined by their relative placement, so that mechanisms can be built out of rather than into the regular components. Because the individual parts are literally finite elements, there is a natural hierarchical decomposition in modeling between that of the part types and their combination in a structure.

Reversibly assembled cellular composites can be considered to be a "digital" material (*27*): A discrete set of parts is linked with a discrete set of relative positions and orientations. These attributes allow an assembler to place them using only local information rather than global positioning, and allow placement errors to be detected and corrected. These attributes are familiar in nanoassembly (*28*) and are used here on macroscopic scales. These materials combine the size and strength of composites with the low density of cellular materials and the convenience of additive manufacturing. The need for custom tooling is eliminated, because parts can be incrementally added to a structure. Their construction, modification, repair, and reuse can all employ the same reversible linking process. Heterogeneous elements can be incorporated in structures with functions determined by their relative placement. Exact assembly of discrete cellular composites offers new properties and performance not available with the analog alternatives of continuously depositing or removing material.

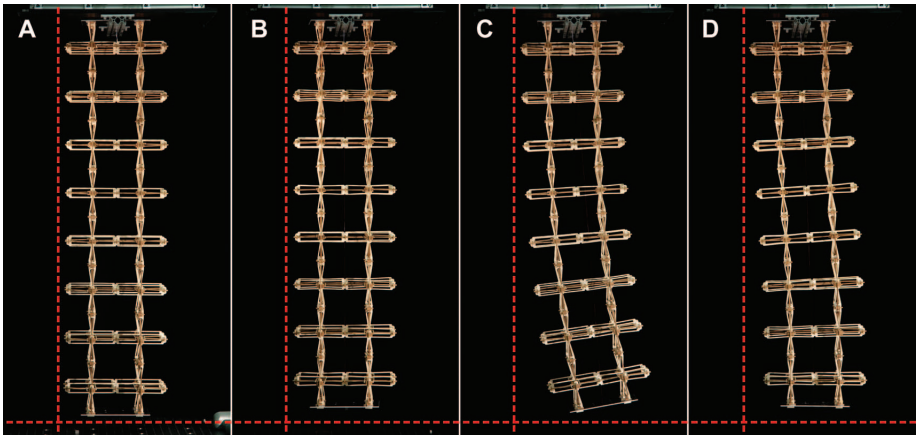


Fig. 4. Deformations designed by the relative placement of rigid and flexural components. Photographs (**A** to **D**) are shown, with initial conditions (A) and red datum lines for comparison. Using identical sets of these two part types, the structures shown (B to D) differ only by the spatial arrangement of these parts. Under identical constraints and loading conditions (provided by a cable running through the center of the structure), we see pure axial compression in one example (B), simple Euler buckling (biased to occur in one direction) in another example (C), and complex buckling in the third example (D). Part placement diagrams and simulations for the differing structures are shown in fig. S6 (*20*).

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Supplementary Materials

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Materials and Methods
Figs. S1 to S8
Tables S1 and S2
References (*29–32*)
Movie S1

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Topotactic Interconversion of Nanoparticle Superlattices

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The directed assembly of nanoparticle building blocks is a promising method for generating sophisticated three-dimensional materials by design. In this work, we have used DNA linkers to synthesize nanoparticle superlattices that have greater complexity than simple binary systems using the process of topotactic intercalation—the insertion of a third nanoparticle component at predetermined sites within a preformed binary lattice. Five distinct crystals were synthesized with this methodology, three of which have no equivalent in atomic or molecular crystals, demonstrating a general approach for assembling highly ordered ternary nanoparticle superlattices whose structures can be predicted before their synthesis. Additionally, the intercalation process was demonstrated to be completely reversible; the inserted nanoparticles could be expelled into solution by raising the temperature, and the ternary superlattice could be recovered by cooling.

Nanoparticles (NPs) functionalized with surface ligands can be assembled into superlattices (SLs), and the physical properties of the resulting macroscopic materials can be tuned by varying the composition, shape, and size of the NPs. Moreover, ligand interactions between particles can be used to control interparticle distances and lattice symmetry (*1*–*4*). However, compared to the compositional diversity and dynamic phase behaviors exhibited in atomic or molecule-based crystalline materials (e.g., alloys or complex oxides), NP SLs are still limited to predominantly one- or two-component systems with structures that can be minimally altered once assembled. Therefore, key challenges in the generation of NP-based materials by design are the development of methods to synthesize increasingly sophisticated lattices and to manipulate lattice structure post-assembly to modify photonic (*5*, *6*), plasmonic (*7*, *8*), magnetic (*5*), and catalytic (*9*) properties that can emerge from assembled arrays of NPs.

To this end, DNA is an ideal ligand for assembling SLs because an oligonucleotide's nucleobase sequence can be used to precisely control the strength, length, and interparticle specificity of bonding interactions (*1*, *2*, *10*–*20*). A set of design rules has recently been developed that allows for a priori determination of the DNA strands necessary to generate a given SL (*1*, *2*), the primary rule being that the thermodynamically favored crystal structure is typically the arrangement of NPs that maximizes DNA hybridization interactions. The number of DNA hybridization events in a given SL can be calculated with the recently developed complementary contact model (CCM) (*1*), enabling accurate predictions of SL stability. Nevertheless, the goal of being able to synthesize multicomponent and dynamic materials is still not fully realized, as NP SLs with more than two components are typically either synthesized in low yield or only in two-dimensional (2D) systems (*21*, *22*), and postsynthetic changes to structure have been limited primarily to modifications of SL lattice parameters (*23*–*25*).

One approach to achieve more complex lattices would be the topotactic insertion of a third nanoparticle component into a preformed binary SL. Topotactic transitions are structural changes to a crystalline solid, where the final lattice is related to the initial lattice by one or more crystallographically equivalent, orientational relationships (*26*). Here, we use the term "topotactic intercalation" to describe the insertion of NPs into a binary SL at predefined positions while preserving the symmetry and quality of the initial structure. More simply, a two-component "parent" SL is synthesized using the previously established design rules, then appended with a third "daughter" NP component (Fig. 1), analogous to the insertion of lithium atoms into a preexisting metal oxide (*27*). This strategy both circumvents many of the possible kinetic structures that could arise from trying to assemble all three NP components simultaneously and provides a means to alter bonding interactions between particles postsynthetically. Herein, we generate five distinct ternary NP SLs by topotactic insertion of particles at programmable positions in a unit cell. Moreover, we demonstrate that these SLs can be reversibly switched between the two-component parent and three-component daughter SLs by raising and lowering the solution temperature.

Each SL was generated by first covalently attaching a dense monolayer of DNA to the surface of a NP and then hybridizing DNA linker strands to the covalently bound oligonucleotides; these building blocks are referred to as nanoscale programmable atom equivalents (PAEs) (*2*). Each

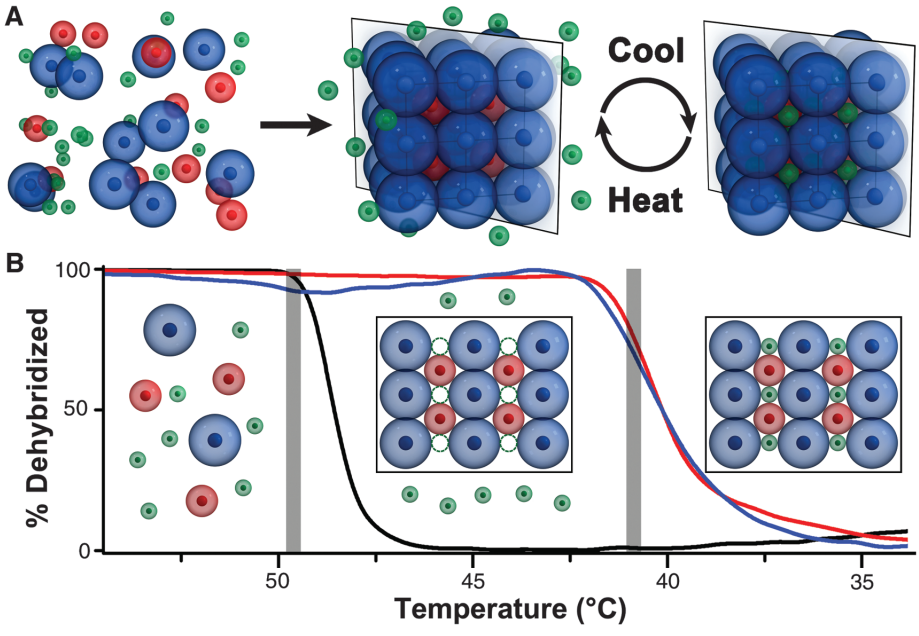


Fig. 1. Scheme of ternary nanoparticle superlattice assembly. (**A**) Ternary NP SLs were obtained by first synthesizing a binary parent SL, followed by the reversible topotactic insertion of a daughter NP into specific, predesigned pockets within the parent lattice. Planes in the middle and right images demonstrate the (110) plane and correlate to the insets in (B). For clarity, individual DNA strands are omitted; the "shell" of multiple DNA strands surrounding each particle is shown as a semitransparent sphere, drawn to scale (see fig. S1). (**B**) Thermal analysis of the temperatures at which the strong parent bonds (black curve) and weaker parent-to-daughter bonds (blue and red curves) form/break. Insets demonstrate which types of bonds are stable in each temperature regime, from high temperatures (no bonds stable), to intermediate temperatures (only parent bonds stable), to low temperatures (all bonds stable). The (110) planes of the parent and daughter SLs are shown as insets, demonstrating how the daughter NP pockets are positioned in the parent SL.

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DNA linker strand contained a sequence complementary to the DNA strands attached to the NP, a nonbinding "spacer" sequence, and a short, terminal "sticky end" that dictated binding interactions between NPs in solution (fig. S1) (*1*, *11*, *28*). Specific, predesigned ternary structures were designed with the CCM to select DNA strands and NPs of appropriate sizes to create a parent cell that contains a programmable "pocket"—a specific site in the parent SL of exactly the right size to fit a daughter NP (Fig. 1, A and B) (the design process is described in detail in the supplementary materials, figs. S2 to S11). When the parent SL and daughter NPs were combined, the daughter NPs were directed toward this pocket, because it was only in this exact position that the number of DNA connections for the daughter NP was maximized.

Each NP in the parent SL bore two different types of linkers. One had a sticky end that formed a strong bond between the parent NPs [ΔG ~60.7 kJ/mol for a single linkage (*29*)], and the other had a sticky end that formed weaker bonds with the daughter NPs [ΔG ~33.5 kJ/mol for a single linkage (*29*)]. The daughter NPs were functionalized with a single type of weak-binding linker that allowed them to bond to the parent SL. This difference in binding strength prevented disruption of the parent SL upon intercalation and created a temperature regime where parent DNA connections were stable but the connections holding the daughter NPs were not (Fig. 1B) (specific temperature regimes are listed in the supplementary materials, figs. S12 to S16).

Our first topotactic intercalation target was a SL with ABC_{12} stoichiometry; this ternary structure has no known atomic equivalent but is related to the binary Cs_6C_{60}-type SL previously studied by our group and others (*1*, *30*, *31*), making it an ideal initial target for this process (see the supplementary materials for DNA and NP design, tables S1 to S4). The parent CsCl-type SL (synthesized with 20-nm gold NPs with ~30-nm DNA linkers, and 15-nm NPs with ~32-nm DNA linkers) was assembled and annealed just below the structure's melting temperature, and the parent SL identity was confirmed using small-angle x-ray scattering (SAXS) (Fig. 2A). Upon confirmation of SL structure, an excess of daughter NPs (in all SLs in this work, the daughter NPs contained a 10-nm gold NP core functionalized with ~8-nm DNA linkers) was added to the solution, and the mixture was cooled ~10°C to a temperature at which DNA connections between the parent lattice and the daughter particles were stable. After a few hours, the supernatant of the solution lightened in color dramatically, indicative of daughter NPs incorporating into the parent lattice. SAXS was then used to confirm not only that the parent SL had taken up the daughter NPs but also that these daughter NPs were positioned exactly as designed, generating the predicted ABC12 structure (Fig. 2A).

To further confirm that the daughter NPs had indeed fully penetrated the parent structures, a sample of the ABC_{12} SL was embedded in silica (*32*), then further encased in a commercially available resin to allow for microtoming and subsequent analysis by transmission electron microscopy (TEM) (Fig. 3A and fig. S18). The TEM images confirm

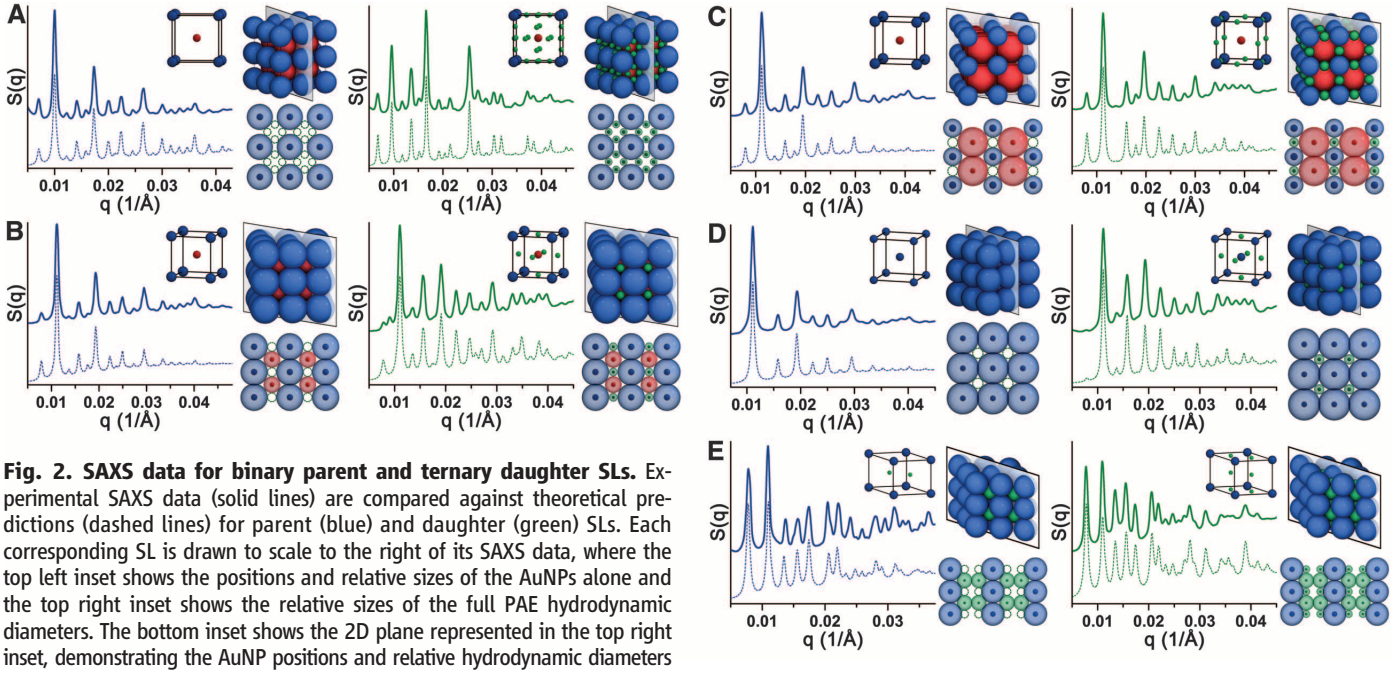


Fig. 2. SAXS data for binary parent and ternary daughter SLs. Experimental SAXS data (solid lines) are compared against theoretical predictions (dashed lines) for parent (blue) and daughter (green) SLs. Each corresponding SL is drawn to scale to the right of its SAXS data, where the top left inset shows the positions and relative sizes of the AuNPs alone and the top right inset shows the relative sizes of the full PAE hydrodynamic diameters. The bottom inset shows the 2D plane represented in the top right inset, demonstrating the AuNP positions and relative hydrodynamic diameters of the particles within that plane. The 2D planes of the parent SLs also show the pockets into which daughter NPs are inserted (dashed green outlines). The parent and daughter SLs are isostructural with (**A**) CsCl and ABC_{12}-type, (**B**) CsCl and face-perovskite, (**C**) CsCl and edge-perovskite, (**D**) bcc and A_2B_3-type, and (**E**) AlB_2- and AB_4-type geometries.

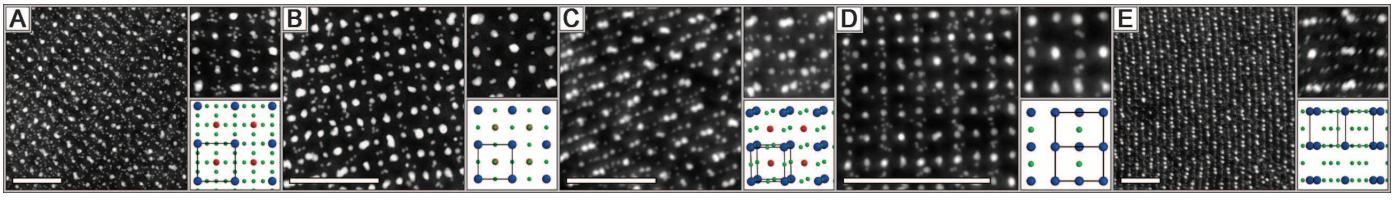


Fig. 3. TEM data for ternary NP SLs. DNA-linked NP SLs were embedded in silica to preserve their structure, then embedded in a commercially available resin and microtomed. TEM images of the microtomed sections show the incorporation of the daughter NPs into the parent SLs, in a lower magnification image (larger image, left), and a higher magnification image (right, top) that shows the SLs viewed along a specific orientation. An image of a modeled SL is provided for comparison (right, bottom) to demonstrate the angle at which the lattices are viewed in the higher magnification images. TEM images are for SLs isostructural with (**A**) ABC_{12}-type, (**B**) face-perovskite, (**C**) edge-perovskite, (**D**) A_2B_3-type, and (**E**) AB_4-type geometries. Scale bars, 200 nm.

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that the daughter NPs infiltrated the entire lattice in high yield. It is important to note that the disordering of daughter NP positions observed by TEM is an artifact only observed after the embedding preparation process (*32*). In their native solution-phase state, the identity of the ABC_{12} SL can be assigned unambiguously by SAXS, and all NPs can be found at the predicted sites within the unit cell (see the supplementary materials for a description of the analysis, figs. S23 and S24).

To prove that topotactic conversions are a general means to achieve complex SLs with multiple NP components, DNA and NP designs were generated for the synthesis of two different perovskite-type SLs, which we have denoted as "face" and "edge" type. We use this terminology because both SLs consist of CsCl-type parent lattices constructed with 20-nm and 15-nm NP cores, but DNA linkers of different lengths were used so that the 10-nm daughter NPs were positioned along either the faces or the edges of a lattice unit cell, as confirmed by SAXS (Fig. 2, B and C) and TEM (Fig. 3, B and C, and figs. S19 and S20) (specific DNA sequences and lengths are listed in tables S2 to S4). Although the parent SLs of these two ternary structures were identical (as defined by the positions and sizes of the gold NPs in the SLs), the DNA linkers allowed the overall hydrodynamic radii of the PAEs to be controlled separately from the sizes of their inorganic cores (Fig. 2, B and C, insets). This enabled us to specifically program where the "pockets" were in a given SL, thereby generating a distinct ternary structure by design, instead of generating an uncontrolled and random arrangement of particles.

We also demonstrated the use of a body-centered cubic (bcc) SL as a parent structure by assembling two sets of PAEs that had different lengths of DNA linker (~35 or ~19 nm) but contained an inorganic core of equivalent size (15 nm). Daughter NPs were added to this bcc parent SL to generate an A_2B_3-type structure (for which no atomic equivalent was identified) (Figs. 2D and 3D, and figs. S17 and S21). This strategy was also applied to lower-symmetry parent lattices by using a hexagonal AlB_2-type SL as a parent structure (20- and 10-nm NPs; unit cell dimensions: $a = 91$ nm, $c = 83$ nm) and adding daughter NPs to generate an AB_4-type SL that also has no atomic equivalent (Figs. 2E and 3E, and fig. S22). Notably, the daughter NPs incorporated into the parent unit cell at the desired positions without substantial alteration to the c/a axis ratio (0.86 to 0.91). This indicates that the parent linkages were indeed strong enough to hold the initial lattice in place during the particle intercalation process, and limited reorganization was necessary to accommodate the daughter NPs, despite the environment within the SL being crowded with both NPs and numerous DNA strands.

In addition to providing a general means to synthesize multicomponent SLs by design, this intercalation process also opens an avenue toward making dynamic structures capable of reversible alterations to their crystal symmetry. Because the linkages holding these daughter particles in place are designed to be thermally addressable at a considerably lower temperature than the linkages in the parent lattice (figs. S12 to S16), we hypothesized that the binary "parent SL" and ternary "daughter SL" states could be easily interconverted by simple changes to the solution temperature. By heating the daughter lattice to a temperature at which only the parent linkages are stable, the highly crowded and charged environment within the lattice would be predicted to expel the daughter particles. The nanoparticles could then be subsequently reincorporated by cooling the system to a temperature where the parent-daughter linkages are once again stable, allowing for cycling between the two different crystal states.

A_2B_3 lattices were used to test this hypothesis, because the addition of daughter NPs breaks the symmetry of the parent bcc SL, generating additional scattering peaks in the SAXS data that provide distinct diagnostic handles to confirm the inclusion or exclusion of the daughter NPs. By heating and cooling the A_2B_3 SL above and below the melting transition of the daughter linkages (42°C), the daughter NPs were easily taken into and subsequently expelled from the parent bcc SL (Fig. 4). The A_2B_3 lattice was taken through three full intercalation/deintercalation cycles without any noticeable loss in crystal quality through simple changes to the temperature of the solution; no stirring was required, and no particles were added or removed at any point during the temperature cycling. Beyond three cycles, the x-ray beam used to characterize the lattices resulted in sample degradation. As proof that this reversibility is not exclusive to the A_2B_3 lattice, an ABC_{12} lattice was also tested and found to exhibit the same completely reversible assembly properties (fig. S25).

The generation of ternary NP SLs through the process of topotactic intercalation pushes the field of nanoparticle-based materials assembly toward the complexity that can be observed in naturally occurring atom- or molecule-based materials, and the ability to alter crystal structure "on the fly" makes them, in principle, ideal components for functional devices that can be toggled between different states. We believe that these two advances promise access to exotic structures with tunable physical properties not accessible with traditional materials synthesis methods such as reconfigurable metamaterials (*7*, *33*) or multicomponent structures composed of greater than two functional elements (*34*) with unique plasmonic (*7*, *8*), magnetic (*5*), or catalytic properties (*9*).

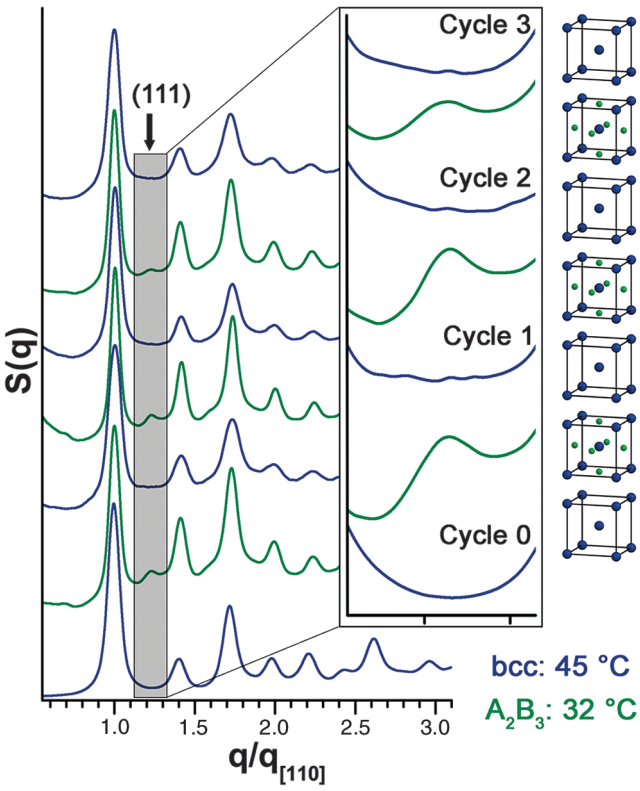


Fig. 4. Reversible intercalation of daughter particles. SAXS patterns of a parent bcc SL (blue curves) and daughter A_2B_3 SL (green curves) were interconverted by raising the temperature of the system above and below the melting transition (42°C). Three complete cycles, starting with the parent lattice at a high temperature (45°C), are numbered from bottom to top. The transition from the parent to daughter states can be noted by the presence or absence of the (111) scattering peak, as can be seen in the inset data. Note that, because the addition of daughter particles breaks the symmetry of the parent lattice, the peak positions are not normalized relative to their first-order scattering peak positions, but relative to their (110) peak positions, noted as a value of 1.0 for all scans.

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Supplementary Materials

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Figs. S1 to S25
Tables S1 to S4
References (*35*, *36*)

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Organotextile Catalysis

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Throughout human history, textiles have been integral to daily life, but their exploration in catalysis has been rare. Herein, we show a facile and permanent immobilization of organocatalysts on the textile nylon using ultraviolet light. The catalyst and the textile material require no chemical modification for the immobilization. All of the prepared textile-immobilized organocatalysts (a Lewis basic, a Brønsted acidic, and a chiral organocatalyst) display excellent stability, activity, and recyclability for various organic transformations. Very good enantioselectivity (>95:5 enantiomeric ratio) can be maintained for more than 250 cycles of asymmetric catalysis. Practical and straightforward applications of textile organocatalysis may be beneficial for various fields by offering inexpensive and accessible functionalized catalytic materials.

Catalysis with small organic molecules has been intensively investigated in recent years, providing distinct reactivity, activity, and selectivity that complement biocatalysis and transition metal catalysis. Organocatalysts are metal-free and display Lewis acidic or basic and Brønsted acidic or basic reactivity (*1*–*3*). Despite fruitful advancements in academia, further application of organocatalysts in industry is often hampered by their relatively low turnover efficiency, even though exceptions exist. The immobilization of organocatalysts via a covalent bonding interaction could provide a general solution, preventing leaching out of catalytically active centers (*4*–*6*). To access heterogeneous organocatalysts, research has focused on immobilizing the catalysts on diverse solid materials (*7*). However, a general and convenient method for the immobilization of different types of organocatalysts that addresses stability, reactivity, and recyclability of the obtained hetereogeneous material has not been established previously.

We recently became interested in identifying inexpensive and abundant polymeric solid materials that would support organocatalysts while displaying various practical advantages, such as high flexibility, durability, versatility, and broad accessibility. Since the early 1930s, by taking advantage of organic chemistry and polymer technologies, synthetic textiles have been produced on a large scale (*8*). However, chemical applications of textile materials have been rare, possibly because of its perceived inertness for further manipulations. We realized the potential of industrially produced textile materials as support for organic catalysts and now report here the preparation and use of several textile-immobilized organocatalysts, which display excellent activity, selectivity, and recyclability.

Textiles have previously been used as solid supports for nanosized components, such as graphene and carbon nanotubes via physical absorption or adhesion (*9*–*12*). In 1935, Bredig *et al*. used amine-functionalized organic fibers (i.e., cellulose and cotton) as catalysts for a cyanohydrin formation reaction (*13*). Recently, a heterobimetallic complex (Pd/Co) was prepared by using wool as a ligand and applied in asymmetric hydration of unsaturated carboxylic acids (*14*). However, as of yet textile materials have not been used as a general solid support for organic compounds in selective catalysis. During our own research, we have found that the irradiation of textiles can result in the photochemical production of surface radicals, which can be used to further functionalize the textile with organic molecules and biocatalysts (*15*–*17*). Therefore, we presumed that this strategy could be applied in a facile preparation of solid-supported organocatalysts under photochemical reaction conditions.

We commenced our study by investigating the immobilization of three representative organocatalysts, a dimethylaminopyridine (DMAP) derivative, a sulfonic acid, and a bifunctional chiral organocatalyst, using nylon as support (Fig. 1). Gratifyingly, all organocatalysts (**1a**, **2**, and **3**) were successfully immobilized on the textile and fully analyzed by various methods (see tables S1 to S5 for immobilization reaction conditions). The catalyst loading can be controlled by adding a cross-linker, such as PETA (penta-erythritol triacrylate) (*18*). Lewis basic catalyst **1a**, Brønsted acid catalyst **2**, and bifunctional organocatalyst **3a**, which possesses both a basic and an acidic functionality, were equally tolerated under the

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photochemical reaction conditions yielding textile catalysts **OrganoTexCat-1a**, **-2** and **-3a** with catalyst loadings of up to 0.025 mmol/g. Irradiation time proved critical for both catalyst loading and catalytic activity (vide infra). A short irradiation time (5 min) for each side of the textile could improve the catalyst loading while preventing any degradation of the textile and the organic catalysts.

Next, the catalytic activity and recyclability of catalyst **OrganoTexCat-1a** was investigated in the acylation reaction of sterically demanding phenol **4** with isobutyric anhydride (Fig. 2A) (*19*). In the absence of catalyst **OrganoTexCat-1a** or in the presence of blank polyamide instead of **OrganoTexCat-1a**, only insignificant background reaction was observed under otherwise identical reaction conditions. After full conversion of starting material **4**, the catalyst was easily recovered by decanting the liquid phase, simply washing with an organic solvent, and drying by blowing air onto the textile. Several recycling experiments revealed the robustness of our catalyst **OrganoTexCat-1a** (Fig. 2B). In more than 10 recycling experiments, no significant erosion of the catalytic activity was observed. The catalyst can be deactivated by forming an acid-base salt with the carboxylic acid by-product of the reaction (fourth run in Fig. 2B). However, the catalytic activity could be readily recovered by washing with triethylamine to regenerate the catalyst with good activity.

In addition to **OrganoTexCat-1**, we prepared several other textile-supported DMAP variants with different linker groups (fig. S4). These Lewis ba-

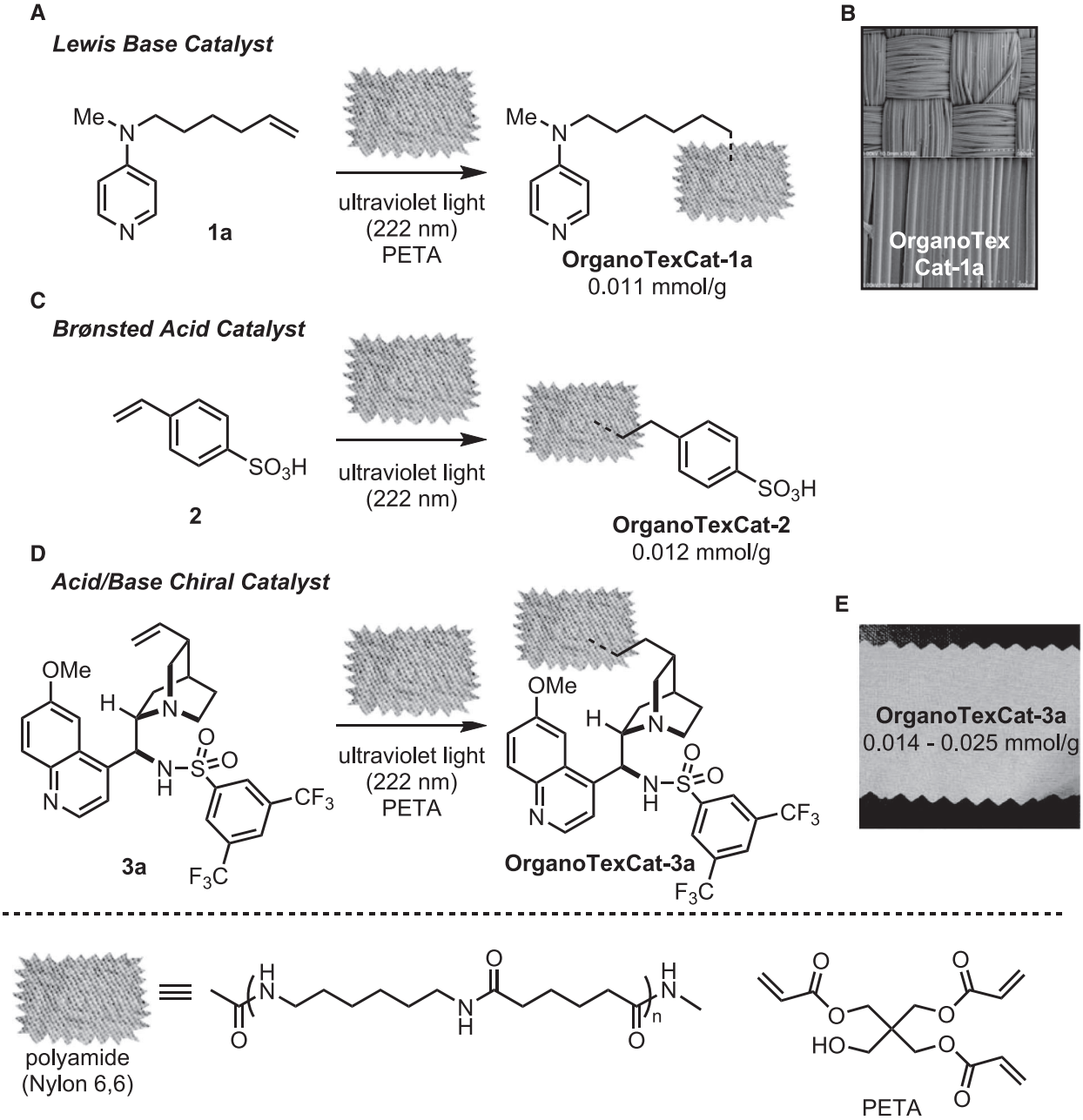


Fig. 1. Reaction conditions for the photochemical immobilization. The textile was irradiated with ultraviolet light for 5 min on each side of the textile wetted by a solution of the organic catalyst. (**A**) Immobilization of DMAP derivative **1a** on textile from an acetonitrile solution. The catalyst loading was determined by acid/base titration. Me, methyl group. (**B**) Scanning electron microscope image of **OrganoTexCat-1a**. (**C**) Immobilization of *p*-styrenesulfonic acid (**2**) on textile from a water/ethanol (1:1) solution. The catalyst loading was determined by elemental analysis. (**D**) Immobilization of bifunctional chiral catalyst **3** on textile from an acetonitrile solution. Catalyst loading was determined by elemental analysis, MAS (magic-angle solid-state) ^{19}F NMR spectroscopy (fig. S1), and XPS analysis (figs. S2 and S3). (**E**) A photograph of catalyst **OrganoTexCat-3a** (numbers indicate the catalyst loading per gram of sheet).

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sic catalysts can also be used in a carbonate-forming reaction from epoxide **6** (*20*). **OrganoTexCat-1d**, which showed the highest activity after optimization of the side chain structure, demonstrated reasonable activity for this reaction in supercritical CO_2 (Fig. 2C). **OrganoTexCat-1d** could be easily recycled and showed identical activity for seven cycles affording cyclic carbonate **7** without considerable formation of polymeric by-products. This result highlights the high stability of the catalyst under high pressure (100 atm) and temperatures (up to 75°C), which might be beneficial for further applications.

Highly Brønsted acidic heterogeneous catalysts are of great interest in industrial chemical production (*21*). As shown in Fig. 2D, acidic **OrganoTexCat-2** displays good activity in an intramolecular hydroetherification, affording the corresponding tetrahydrofuran in excellent yield. No background reaction was observed in the absence of the catalyst. The immobilized acidic catalyst is easy to handle and features robust stability for the transformation, which are the primary advantages of polymer-supported catalysts.

After establishing a facile immobilization methodology for organocatalysts on textile materials and applying them successfully to three different classes of transformations, we turned our attention to asymmetric catalysis. Although various attempts have been made to provide heterogeneous chiral organocatalysts, they typically give inferior stereoselectivity, possibly because of the alteration of the microenvironment of the catalytically active sites (*22*, *23*).

Cinchona alkaloids, naturally occurring chiral molecules with various functional groups, have emerged as privileged ligands and organocatalysts for various catalytic asymmetric transformations (*24*). With *cinchona*-sulfonamide–based **OrganoTexCat-3a** in our hands, we evaluated activity and recyclability by performing the alcoholytic desymmetrization of cyclic anhydride **10** (*25*–*27*). **OrganoTexCat-3a** showed a very similar enantioselectivity [96.5:3.5 enantiomeric ratio (er)] to homogeneous catalyst **3a** (97:3 er) although requiring a somewhat longer reaction time (Fig. 3A).

After the photochemical preparation of catalyst **OrganoTexCat-3a**, residual homogenous catalyst **3a** could be recovered and reused for subsequent immobilization reactions (figs. S5 and S6). Furthermore, the robustness of **OrganoTexCat-3a** is illustrated with hundreds of recycling experiments (Fig. 3B). By varying the reaction conditions, such as the amount of nucleophile and the concentration of the substrate, we obtained an optimal enantioselectivity (er up to 97:3). This result is comparable to the homogeneous reaction conditions with 5 to 10 mole percent (mol %) of catalyst loading of **3a**. Moreover, the catalyst loading could be decreased to 4 mol % without loss of enantioselectivity (77th to 81st cycles). To investigate the fate of our catalyst, we conducted further recycling experiments by using 6 mol % of the catalyst, and the desired product was obtained with more than 95:5 er without erosion of enantioselectivities for more than 220 cycles. After 200 cycles, a slight deactivation of **OrganoTexCat-3a** was observed and resulted in a lower enantioselectivity (94:6 er). However, increasing the catalyst loading to 10 mol % led to an increase of the enantioselectivity back to 95:5 er (231st cycle). Therefore, we concluded that the chemical structure of the chiral catalyst was indeed intact. The loss of activity and enantioselectivity could be ascribed to the detachment of a certain amount of the catalytically active species from the textile after more than 300 recycling experiments in the presence of excess of methanol.

The substrate scope of **OrganoTexCat-3a** for the desymmetrization of different *meso*-anhydrides has also been determined and is summarized in Fig. 4A. Various *meso*-anhydrides were smoothly transformed into enantioenriched hemiesters with excellent yields (up to 99%) and enantioselectivities (er up to 97:3). Bi- and tricyclic compounds could also be used to afford the desired products with high enantioselectivities and comparable selectivity to the homogeneous catalysis conditions. Moreover, product **11h**, a valuable precursor of statin derivatives (*27*), could be obtained on a gram scale by using a flow reactor with an **OrganoTexCat-3a** packed column in an iterative continuous reaction (Fig. 4B). The column was prepared without any sophisticated packing procedure, contrary to powder- or resin-based heterogeneous catalysts. The textile material showed

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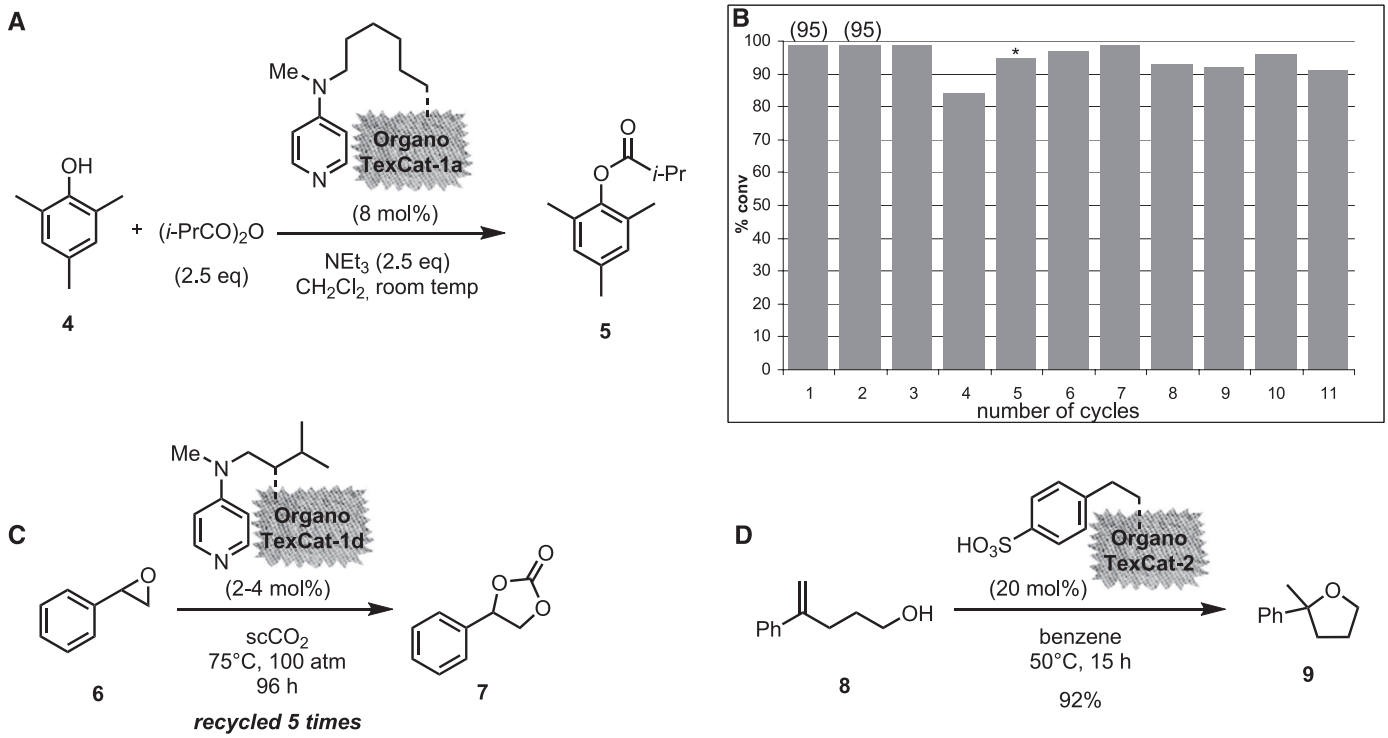


Fig. 2. Reactions using textile-supported achiral catalysts. (**A**) Acylation reaction of phenol **4** to ester **5**. Et, ethyl group; Ph, phenyl group; *i*-Pr, isopropyl; eq, equivalent. (**B**) Recycling experiments of **OrganoTexCat-1a** (reaction conditions: 8 mol % of catalyst loading, 36 hours in CH_2Cl_2, [4] = 0.05 M). The numbers in the parentheses are isolated yields of the acylated product. *After the fourth cycle, each experiment was conducted with the triethylamine-washed textile catalyst. (**C**) A carbonate-forming reaction catalyzed by **OrganoTexCat-1d**. $scCO_2$ indicates supercritical CO_2 reaction conditions. (**D**) A hydroetherification reaction using acidic **OrganoTexCat-2**.

good absorption ability for organic solvents, which can facilitate mass transfer onto the material, generating a microfluidic environment via capillary action to increase the effective catalyst concentration. As shown in Fig. 4C, enantioenriched product **11h** was obtained in quantitative yield (>99% yield) and excellent enantioselectivity (up to 97:3 er) by taking advantage of a simple fixed-bed reactor setup (*28*, *29*). After full conversion of the starting material, the column was washed with methyl *tert*-butyl ether (MTBE) and reused 10 times, showing identical activity and enantioselectivity.

In addition to the robustness of our organotextile catalysts, several aspects should be highlighted. Compared with polymer films, textile fibers exhibit a much higher surface area. The inherent capillary action of textiles allows an easy and uniform wetting of the material with the catalyst before the photoinduced immobilization. This leads to a uniform three-dimensional coating. Moreover, the active surface area is easily adjustable by varying the fiber diameter, which should ultimately enable preparation of organotextiles with significantly higher catalyst loadings. The flexible construction of fabrics allows reactor constructions of arbitrary geometry and a quick removal of the catalyst. Our results underscore the vast potential of supported organocatalysts for chemical synthesis (*30*).

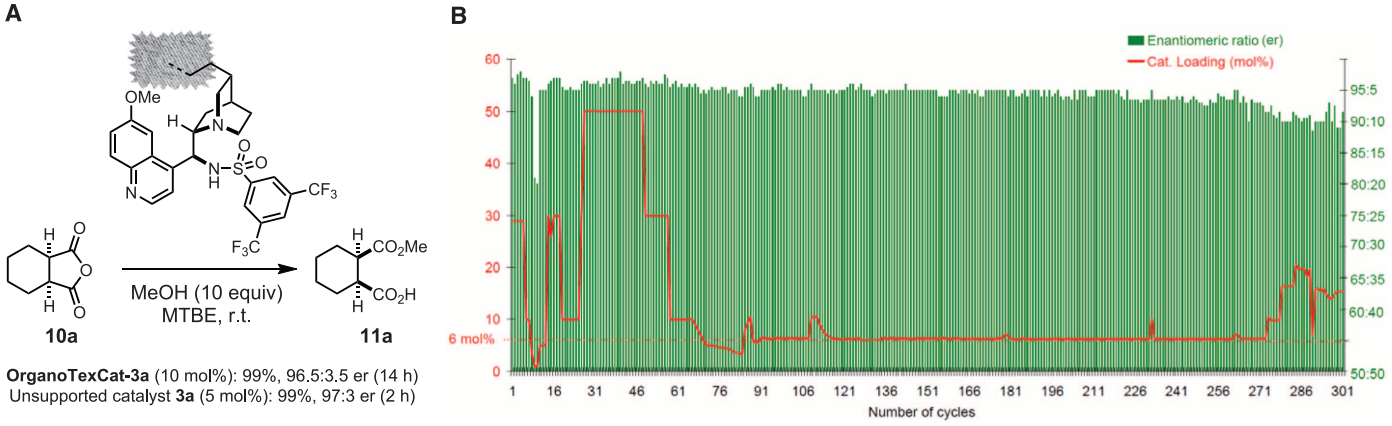


Fig. 3. Performance of the textile-supported chiral catalyst. (**A**) Comparison of the activity of homogeneous catalyst **3a** and heterogeneous **OrganoTexCat-3a**. r.t., room temperature. (**B**) Recycling experiments. For experimental details, see table S6.

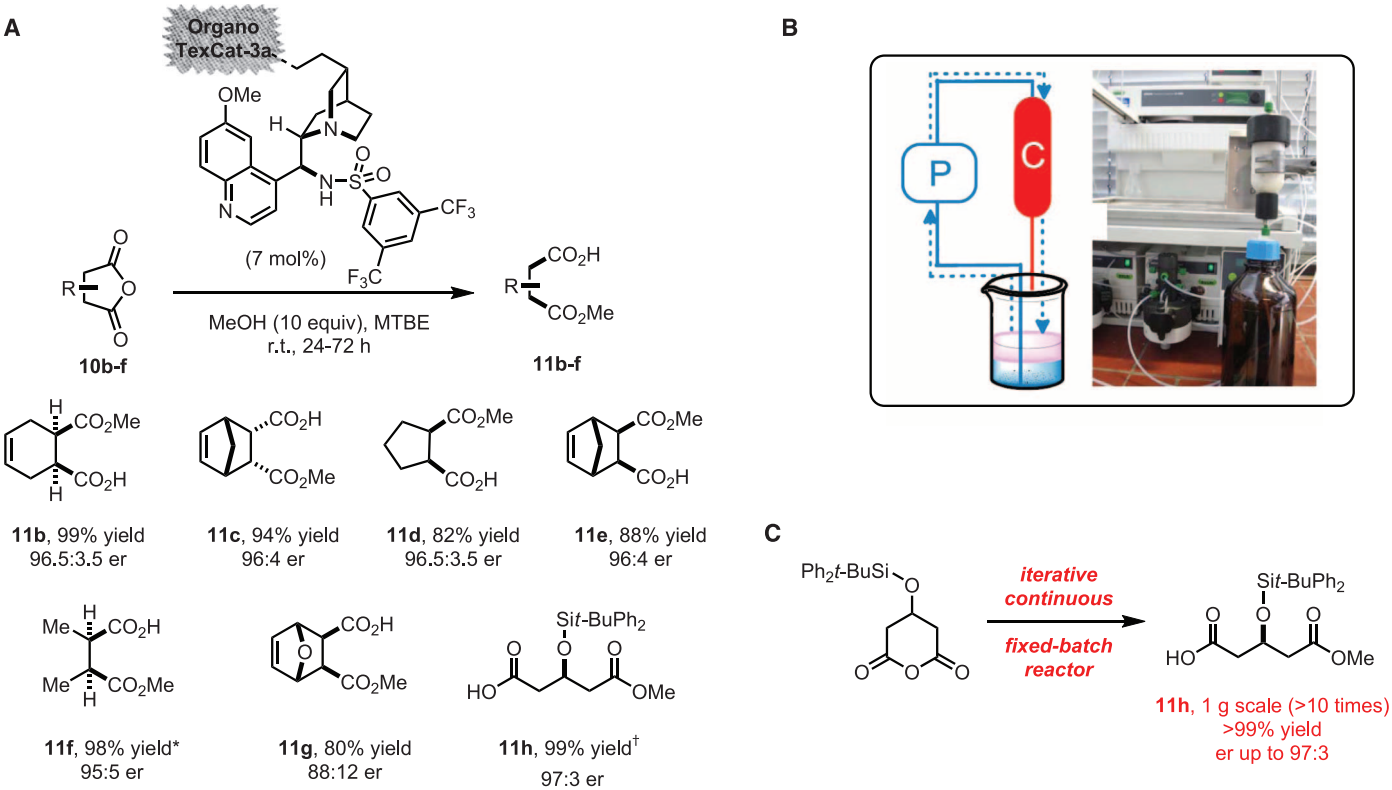


Fig. 4. Substrate scope and applications of OrganoTexCat-3a. (**A**) Substrate scope of the desymmetrization of anhydrides **10** catalyzed by textile **OrganoTexCat-3a**. *15 mol % of catalyst **OrganoTexCat-3a** was used. †50 mol % of catalyst **OrganoTexCat-3a** was used. (**B**) Schematic illustration of the continuous circle reactor and the picture of the reaction setup. P, pump; C, column packed with **OrganoTexCat-3a**. (**C**) Desymmetrization of silylated glutamic anhydride; see table S7 and fig. S7 for the optimization of reaction conditions. *t*-Bu, tertbutyl.

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Supplementary Materials

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Slow Earthquakes, Preseismic Velocity Changes, and the Origin of Slow Frictional Stick-Slip

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Earthquakes normally occur as frictional stick-slip instabilities, resulting in catastrophic failure and seismic rupture. Tectonic faults also fail in slow earthquakes with rupture durations of months or more, yet their origin is poorly understood. Here, we present laboratory observations of repetitive, slow stick-slip in serpentinite fault zones and mechanical evidence for their origin. We document a transition from unstable to stable frictional behavior with increasing slip velocity, providing a mechanism to limit the speed of slow earthquakes. We also document reduction of *P*-wave speed within the active shear zone before stick-slip events. If similar mechanisms operate in nature, our results suggest that higher-resolution studies of elastic properties in tectonic fault zones may aid in the search for reliable earthquake precursors.

Slow earthquakes represent one mode of the spectrum of fault slip behaviors ranging from steady aseismic slip at plate tectonic rates (a few millimeters per year) to normal earthquakes with rupture propagation at a few kilometers per second and fault slip speeds of 1 to 10 m/s, which is consistent with elastodynamic theory (*1*–*6*). Like normal earthquakes, slow earthquakes can accommodate most of a fault's slip budget, with equivalent magnitudes of 8 or larger; yet, this slip occurs slowly, over days to years, rather than the few tens of seconds for normal earthquakes (*1*–*4*). Slow earthquakes often occur adjacent to traditional seismogenic zones (*5*, *7*) and may load these earthquake-prone areas. Moreover, recent work suggests that slow earthquakes may abet potentially devastating earthquakes, such as the 2011 M_w 9 Tohoku Oki earthquake (*7*), and thus, understanding the physics of slow earthquakes and identifying possible precursory changes in fault zone properties are increasingly important goals.

Although observations of slow earthquakes abound, the underlying processes that produce these self-sustaining, quasi-dynamic ruptures remain poorly understood (*3*–*8*). A particularly vexing aspect of slow earthquakes is the mechanism that limits slip speed yet allows self-sustained rupture propagation. One possibility is that slow earthquakes represent prematurely arrested normal earthquakes with slip-speed limited by a mechanism such as dilatant hardening or a transition in friction constitutive behavior with increasing slip speed. Several mechanisms have been proposed (*4*–*12*), but the origin of slow earthquakes remains elusive. Additionally, if slow earthquakes initiate like normal earthquakes they may exhibit precursory effects, such as accelerating fault slip or changes in elastic wave-speed within the rupture nucleation region.

Here, we describe laboratory observations of fault-zone materials showing repetitive, slow stick-slip friction events that are reminiscent of slow earthquakes (Fig. 1). We sheared layers of lizardite-rich serpentinite at constant normal stress of 1 MPa (supplementary text). Each experiment includes 50+ stick-slip events, with durations ranging up to 35 s (Fig. 2). Our experiments show that the laboratory fault zones undergo a transition from velocity-weakening to velocity-strengthening friction behavior above slip rates of ~10 μm/s (Fig. 3). During each slip event, the fault zone shows large changes in elastic wave speed (2 to 21% decrease), with precursory changes of 1 to 3% starting up to 60 s before failure (Fig. 4).

Like natural earthquakes, fault slip velocity during stick-slip events exceeded the imposed far-field velocity. The full record for one experiment shows the character of stress drops and the corresponding stair-step pattern of fault displacement (Fig. 1A). Stick-slip events have durations of 1 to 35 s, average slip velocities of 15 to 280 μm/s, average displacements of 10 to 900 μm, and evolve from small to large events with increasing shear (Fig. 1B). We observed slow stick-slip events at a range of loading velocities (Fig. 2). Each event generally released tens of kilopascals of shear stress—roughly a 5 to 10% stress drop (Fig. 1A). Maximum slip velocities ranged from 60 to 1300 μm/s, but peak velocities were generally sustained for <1 s, with longer acceleration and deceleration periods (Fig. 2B). The events resemble results from experiments conducted on halite (*12*) but are distinguished by their consistent, repetitive nature.

To investigate the processes responsible for these slow-slip events, we conducted additional experiments under stiff loading conditions, including slide-hold-slide (SHS) (fig. S2) and velocity-step tests (fig. S3). We determined the friction rate parameter (a-b = $\Delta\mu/\Delta \ln V$, where V is the velocity) and critical slip distance (D_c) using standard techniques (*13*). With increased shear strain and hold time, (a-b) generally decreased, and D_c increased (fig. S2A). At slip velocities

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of ≤1 μm/s, SHS tests yielded (*b*-*a*) values of 0.2 to 0.002 (Fig. 3), D_c of 5 to 105 μm, and thus values of the critical stiffness from 2.1 to 11.4 kN/mm, which exceeded the elastic stiffness of the loading system (fig. S2A). These (*b*-*a*) values are large compared with typical values for other materials (*13*–*15*). At higher velocities (3 to 1000 μm/s), velocity-step tests indicate (*a*-*b*) from −0.004 to +0.018. Taken together, Fig. 3 shows that lizardite-rich serpentinite transitions from velocity-weakening, −(*a*-*b*), to velocity-strengthening, +(*a*-*b*), frictional behavior above a threshold velocity of ~10 μm/s (Fig. 3 and fig. S3). Previous works on lizardite at slip velocities ≤10 μm/s show primarily velocity-weakening friction (*14*, *15*), which is consistent with our results. At higher normal stress, lizardite continues to show velocity weakening above 10 μm/s (*14*, *15*), which may indicate that the transition from −(*a*-*b*) to +(*a*-*b*) with slip speed only occurs at low effective stresses. A similar transition has been documented for halite (*12*), which was attributed to changes in asperity contact geometry and shear fabric. The frictional properties of lizardite serpentine are distinct from antigorite and chrysotile serpentine (*14*–*17*), which exhibit +(*a*-*b*) at low velocities and transition to −(*a*-*b*) at velocities above ~0.1 μm/s (*15*, *16*), with dramatic weakening at higher slip rates (*17*).

Our experiments included elastic wave-speed measurements, in which *P*-wave flight time increased during stick-slip events, with precursory excursions starting up to 60 s before failure (Fig. 4). Changes in *P*-wave flight time (T_{fl}) for a complete experiment, determined from early *P*-wave coda, are shown in Fig. 4A along with the fault layer thickness and shear stress. The detailed flight time changes for each stick-slip event (Fig. 4B) are superimposed on long-term trends (Fig. 4A) derived from factors such as changes in grain contact stiffness and coordination number, shear fabric development, and layer thinning (*13*, *18*, *19*). Correlation coefficients and pick fidelity decreased late in the experiment (Fig. 4A) because of increased sample attenuation (fig. S1).

Nine stick-slip events highlight T_{fl} changes before each event (Fig. 4B, inset), measured from peak stress. With up to ~0.2 μs flight time increase, absolute *P*-wave velocity (V_P) of the fault layers decreased by 2 to 21% during these events (Fig. 4B). After each slip event, T_{fl} recovered with log time, and in many cases, the original flight time was recovered within 100 s (Fig. 4C). Before failure, T_{fl} increased by up to 0.06 μs, accounting for 10 to 25% of the total V_P change during failure (Fig. 4B). These preseismic flight time changes occurred in tandem with, and were perhaps driven by, ultra-slow preseismic slip (fig. S4).

Our measurements indicate that serpentinite exhibits the necessary and sufficient conditions for dynamic earthquake rupture: −(*a*-*b*) and $k < k_c$ (Fig. 3 and figs. S2 and S3). Friction theory in-

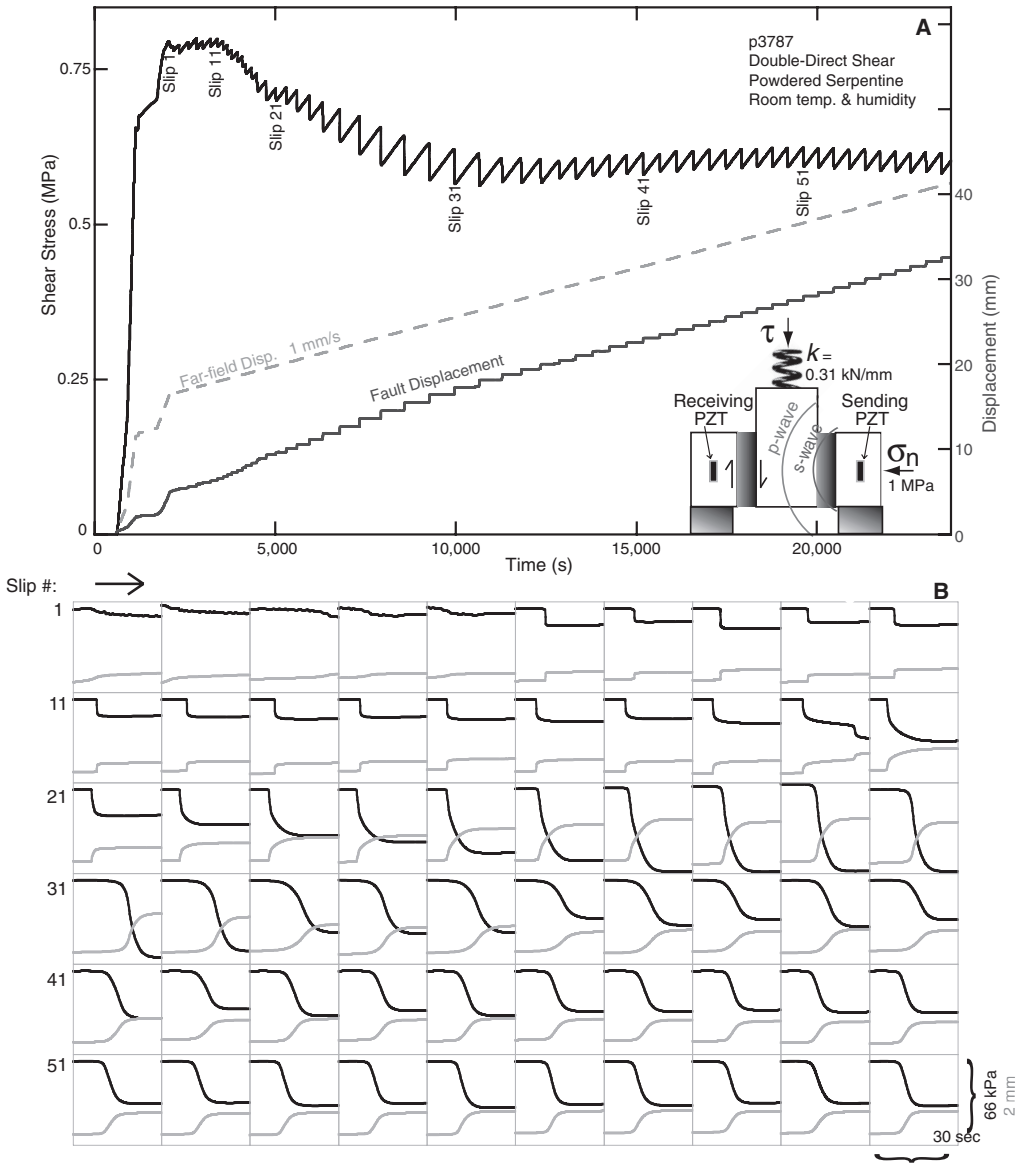


Fig. 1. A full experiment showing repetitive, slow stick-slip. (**A**) Shear stress (τ; top solid line) during repeating stick-slip failure of serpentinite gouge under constant far-field velocity (dashed line). Like earthquake cycles, τ builds over long periods but is released in punctuated slip events, creating steps in fault slip displacement. (Inset) The double-direct shear arrangement with the piezoelectric transducers (PZT). (**B**) Subplots show 30-s windows for each stick-slip event in (A), with event durations from 1 to 30 s. Fault slip (gray lines) is driven by stress release (black lines). There is a clear progression from small impulsive events to large slow events with increasing net displacement.

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dicates that stick-slip initiates when shear stress (τ) exceeds fault strength and the rate of friction weakening exceeds the elastic unloading stiffness. To generate a large, dynamic earthquake rupture, the conditions for instability must persist as slip accelerates and the rupture expands. This requires fault weakening as slip velocity increases, which we observed at low slip velocities (Fig. 3). At higher velocities, serpentinite transitions to velocity-strengthening behavior (Fig. 3 and fig. S3), which causes deceleration and limits fault slip velocity (Fig. 3, inset). During stick-slip events, slip arrests after τ becomes smaller than fault strength. Thus, larger (*b*-*a*) values yield larger stress drops, perhaps explaining the large events at higher strains (Figs. 1 and 3).

Although these experiments do not include the full range of seismogenic conditions and fault zone fluid chemistry (*13*, *15*), they indicate that slow earthquakes could result from the rate-dependent frictional behavior of the fault gouge itself (*3*, *9*). Unlike previous examples of slow laboratory stick-slip with long durations (*12*), the mechanism we document is not limited to a specific fault stiffness and thus may be applicable to a wide range of fault conditions. Our results do not preclude other mechanisms for slow slip (such as dilatant hardening, dehydration reactions, slip weakening, and limited unstable fault area) (*4*–*12*). Our results are consistent with the observation that slow earthquake slip can occur over a range of fault velocities (*4*), suggesting the existence of a spectrum of seismic moment-release rates, dictated primarily by the transition between velocity-weakening and velocity-strengthening friction (Fig. 3) modulated by fault zone conditions.

Existing studies of rupture nucleation (*21*, *22*) show that variations in initial stress and fault strength can cause a range of dynamic rupture propagation rates and nucleation times (*23*). Our observations of slow slip provide an additional mechanism for slow rupture propagation, one that can also account for reproducible, periodic events.

Earthquakes involve fracturing and frictional failure, which commonly affect the elastic properties within the fault zone and surrounding rock (*24*, *25*). Friction data and instability theory indicate that quasi-static slip within the fault zone should initiate before earthquake nucleation (*26*). One expects that this preseismic deformation will produce changes in fault properties such as elastic wave speed; however, there are few reliable observations of precursory changes before earthquake rupture (*24*). If most elastic changes occur within and directly adjacent to the fault zone, fault zone proximity may be a key limitation for many past, regionally focused studies (*25*).

Niu *et al*. (*28*) studied elastic wave speeds immediately adjacent to the San Andreas Fault and observed coseismic changes with apparent precursors (*24*). Our study also benefits from close fault proximity, and we observed large V_P changes (up to 20%), along with precursors that account for 10 to 25% of these changes starting up to 60 s before failure (Fig. 4). After failure, elastic velocity recovers with log time (Fig. 4C), which is consistent with field observations (*25*) and extensive laboratory studies of frictional healing (*6*, *13*, *27*). Precursory V_P changes are most likely tied to preseismic slip and nucleation of instability, as indicated by precise measurements of fault slip (fig. S4). Initial slip likely reduces V_P by a combination of dilation, damage to grain contacts, and grain fracture (*18*, *24*–*29*). Our observations of elastic wave speed are consistent with granular dilation during stick-slip and associated changes in stress state, grain coordination number, and grain contact quality (*18*, *28*–*30*), which evolve with shear deformation (*19*). These observations suggest that a renewed focus on field studies of temporal variations in elastic wave speed may be warranted in regions of high seismic hazard and that a combination of slow slip monitoring and elastic wave speed measurement may provide a basis for reliable earthquake prediction in regions where damaging, normal earthquakes are triggered by slow fault slip.

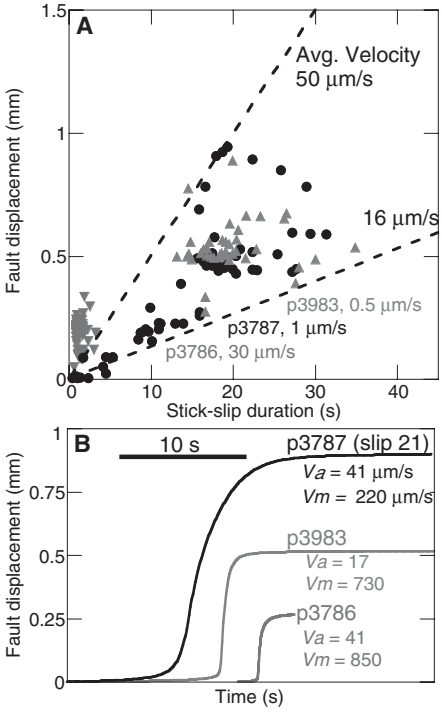


Fig. 2. Stick-slip duration and fault displacement. (**A** and **B**) Repetitive slow stick-slip occurred over a range of driving velocities in three experiments under otherwise identical conditions (circles, p3787, 1 μm/s; inverted triangles, p3786, 30 μm/s; triangles, p3983, 0.5 μm/s). Average slip velocities (V_a) ranged from ~15 to 280 μm/s, with ~15 to 50 μm/s at slower driving velocities. (B) Details of slip acceleration history for representative stick-slip events. Maximum slip velocities (V_m) ranged from 60 to 1100 μm/s, but the fastest velocities were only sustained for short periods (<1 s). Acceleration and deceleration periods often lasted 10+ s, resulting in low average velocities.

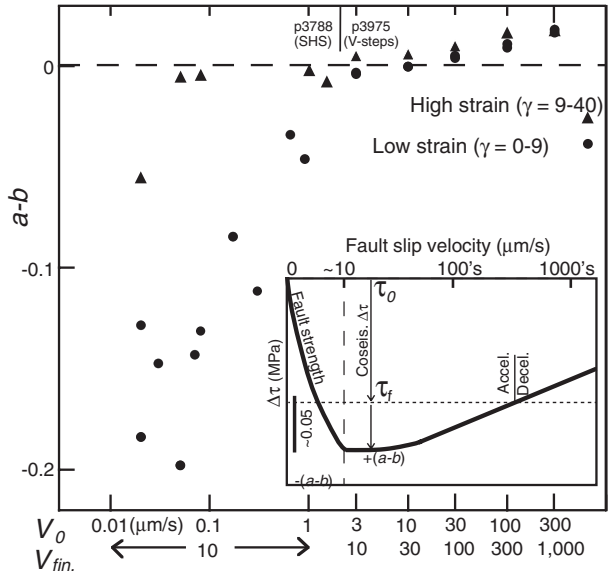


Fig. 3. Frictional strength of serpentine with fault slip speed. Velocity weakening, −(*a*-*b*), occurs at low velocities (≲10 μm/s), which is a necessary condition for earthquake initiation. At higher velocities, lizardite-rich serpentinite becomes velocity-strengthening, which would retard unstable slip. These (*a*-*b*) values were determined from SHS tests (fig. S2) and velocity stepping tests (V-steps) (fig. S3), with initial (V_0) and final ($V_{fin.}$) imposed slip velocities shown on the *x* axis. (**Inset**) A theoretical model for coseismic slip history. Fault slip begins when shear stress (τ_0) exceeds fault strength and accelerates until shear stress drops below fault strength. The observed transition in friction rate dependence means that fault slip decelerates above a threshold velocity. With continued coseismic stress release, slip velocity decreases to balance τ and fault strength, causing slow deceleration and rupture arrest.

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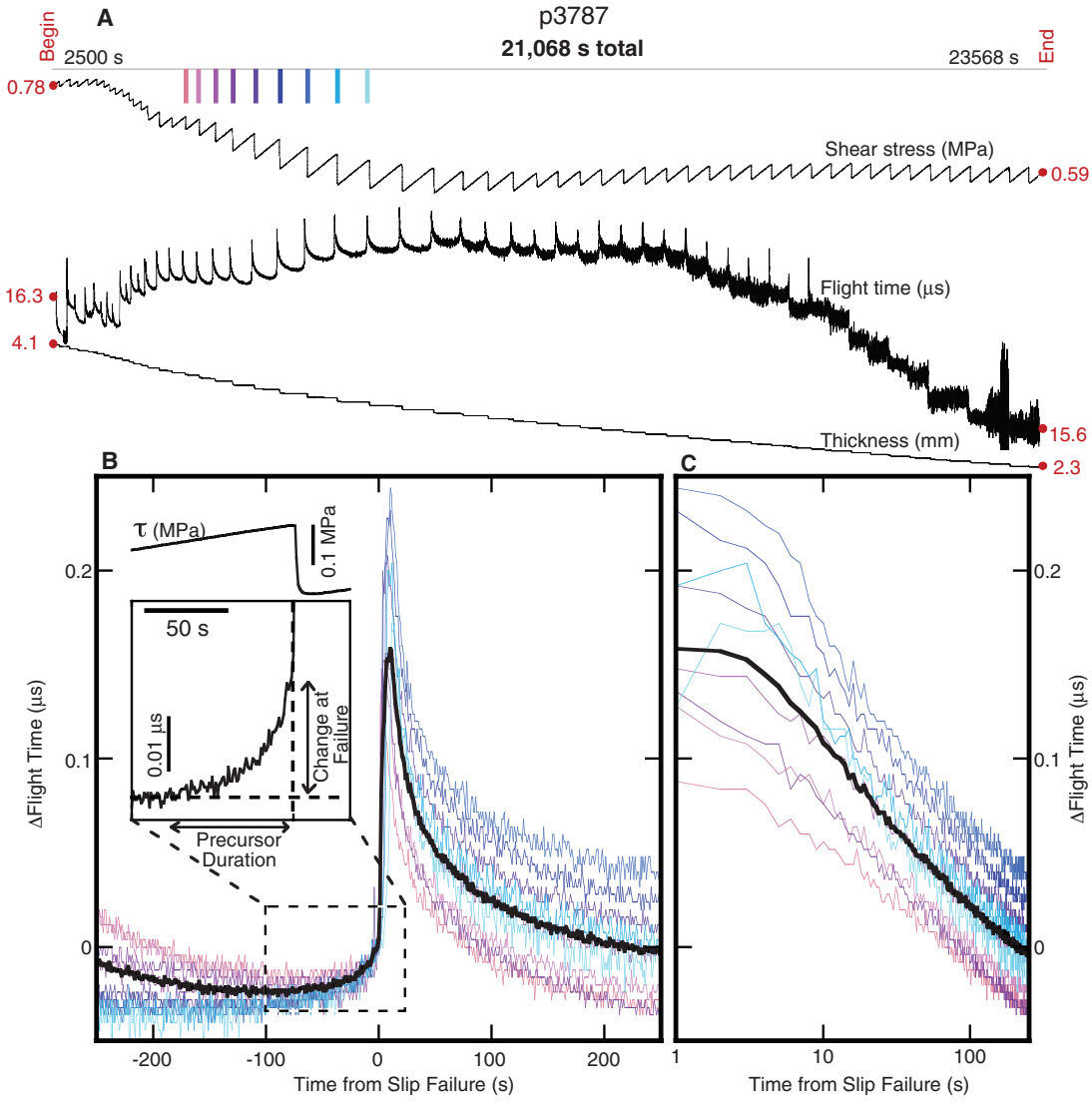


Fig. 4. Preseismic and coseismic elastic wave-speed decrease and postseismic healing. (**A**) Shear stress, fault thickness, and T_{fl} throughout experiment p3787. With each slip event, T_{fl} increases and gradually recovers. (**B**) Highlights of nine sequential events [identified by color dashes in (A)] chosen for low noise and long recurrence intervals. We stacked these events (black line) so as to enhance signal over noise. After peak stress, T_{fl} changes were large, accounting for changes in V_P of up to 2 to 21%; however, 10 to 25% of this decrease occurred before failure. Velocity changes preceded the main shear failure by up to 60 s (inset). (**C**) After each slip event, T_{fl} recovered with log time, indicating fault-healing after rupture (*1*, *13*, *20*, *23*); 75% of baseline velocity was generally recovered after ~100 s.

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Supplementary Materials

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HONO Emissions from Soil Bacteria as a Major Source of Atmospheric Reactive Nitrogen

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Abiotic release of nitrous acid (HONO) in equilibrium with soil nitrite (NO_2^-) was suggested as an important contributor to the missing source of atmospheric HONO and hydroxyl radicals (OH). The role of total soil-derived HONO in the biogeochemical and atmospheric nitrogen cycles, however, has remained unknown. In laboratory experiments, we found that for nonacidic soils from arid and arable areas, reactive nitrogen emitted as HONO is comparable with emissions of nitric oxide (NO). We show that ammonia-oxidizing bacteria can directly release HONO in quantities larger than expected from the acid-base and Henry's law equilibria of the aqueous phase in soil. This component of the nitrogen cycle constitutes an additional loss term for fixed nitrogen in soils and a source for reactive nitrogen in the atmosphere.

Soil biogenic NO emissions account for ~20% of the total NO sources to the atmosphere (*1*) and vary as a function of microbial activity and physicochemical soil properties. NO is produced during nitrification, in which soil microbes convert ammonium (NH_4^+) via NO_2^- to nitrate (NO_3^-), both of which can accumulate in soil (*2*, *3*). In addition, the reduction of NO_3^-, which is known as denitrification, can cause a release of NO. The two microbial processes are mainly influenced by temperature, soil water content, pH value, and mineral nitrogen availability in the soil (*4*–*6*). Previous studies have shown that HONO may also be emitted from soil; this release may originate from the transformation of soil NH_4^+ to NO_2^- (*7*) or from soil NO_2^- because of a chemical acid-base equilibrium (*8*).

To estimate the contribution of soil HONO emissions to the total reactive nitrogen flux (HONO + NO) from the soil to the atmosphere and to elucidate the major processes influencing HONO release from soil, we studied the relation of soil HONO emissions to biogenic soil NO emissions under controlled laboratory conditions using the dynamic chamber method (*9*, *10*). Earlier studies have shown that results from using this technique are consistent with those from field measurements (*9*, *11*, *12*). We investigated soils from various ecosystems around the world, covering a wide range of soil pH, organic matter, and soil nutrient contents (table S1). The soil samples were wetted in order to reach water holding capacity (WHC) (*10*) and placed into the chamber, which was then continuously flushed with purified air (free of HONO, NO_x, O_3, hydrocarbons, and water vapor), leading to a slow drying of the soil sample during the course of the experiment. The gas-phase mixing ratio of HONO released by the soil sample was measured at the chamber exit with a long path absorption photometer (LOPAP) (*13*). Mixing ratios of NO and water vapor were also measured (*14*).

The characteristic moisture dependency of HONO and NO fluxes that is known from previous studies of soil biogenic NO emissions is shown in Fig. 1 (*4*, *9*, *15*, *16*). We found that the maximal emission fluxes of HONO and NO [henceforth denoted as optimum fluxes; $F_{N,opt}$(HONO) and $F_{N,opt}$(NO)] are of comparable magnitude and occur at similar optimum soil water content (SWC) (*10*)—within 10% WHC of one another for all investigated samples.

Chemical acid-base equilibrium calculations predict that abiotic HONO emissions from soil nitrite should be largest for soils with low pH and high NO_2^- content (*8*). The soil pH reflects a sum parameter, which depends on the amount of acidic and basic species in soil, and regulates the solubility of soil constituents and the protonation equilibria. These variables, however, also influence nitrifier and denitrifier activity in soil. In general, abundance and diversity of bacteria are positively correlated with pH (*17*), and individuals mostly possess a maximum activity at a certain pH (*18*). In contrast to expectations based on the acid-base equilibrium, the results from different soil samples presented in Fig. 2 do not show a decrease of HONO fluxes with increasing pH. In fact, the neutral soil sample S12, taken from a wheat field in Germany, features extremely high values for HONO and NO emissions ($F_{N,opt}$: 257.5 ± 0.1 ng m^{-2} s^{-1} HONO, 134.8 ± 0.6 ng m^{-2} s^{-1} NO). The second highest emission of HONO and NO was found for the alkaline, sodic soil represented by sample S17. Comparison with soil NO_2^- and NH_4^+ concentrations (Fig. 2) clearly demonstrates that high HONO and NO emissions are favored for soils with high nutrient content.

The ratio of $F_{N,opt}$(HONO) to $F_{N,opt}$(NO) was found to be higher for arid and arable soils (on

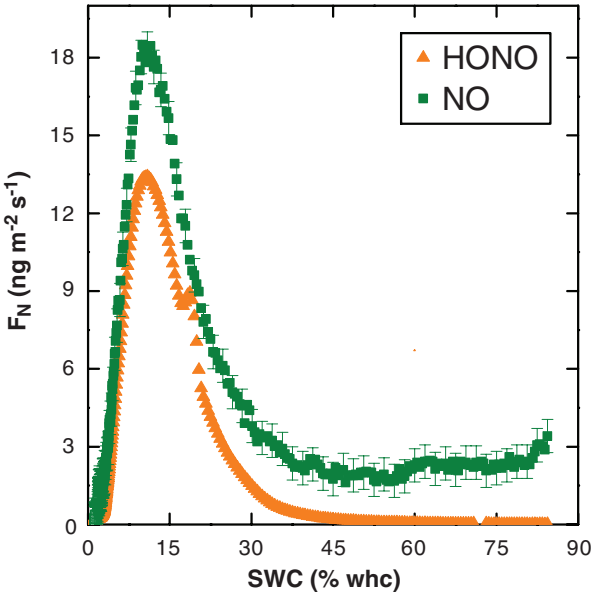


Fig. 1. Soil emissions of HONO and NO feature similar optimum curves. Characteristic HONO (triangles) and NO (squares) emission fluxes (F_N, in terms of nitrogen mass) from soil sample S15 (jujube field, semi-arid, fertilized, and irrigated; Mingfeng, Xinjiang, PR China) as a function of SWC expressed in percent of WHC. Experimental error bars (*10*) are shown for every fourth data point for NO. Error bars of HONO fluxes have the size of the symbols and were omitted.

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average 1.06 ± 0.44) than for nonarable soils of humid and temperate regions (on average 0.16 ± 0.12) (fig. S1). For soil pH values higher than 7, the optimum HONO emission fluxes always exceed 5 ng m^{-2} s^{-1} (in terms of N) and even reached ~258 ng m^{-2} s^{-1} (at 25°C). We anticipate that HONO emissions are particularly relevant for arid and arable areas with neutral or alkaline soil pH, where they may substantially influence tropospheric chemistry. Potential HONO soil emission hot spots comprise, for instance, large areas of northern Africa, central/southwestern Asia, and North America as well as some regions around the Mediterranean Sea (fig. S2), covering in total ~20% of the terrestrial surface (excluding Antarctica). Given the high spatial variability of soil properties (such as pH and nutrients) and our limited amount of soil samples, these hot spot areas may be even larger. This previously neglected ground source of reactive nitrogen may explain the unexpectedly high daytime HONO mixing ratios observed in many studies (*19*). In addition, NO is produced on a time scale of ~30 min from the photolysis of HONO during daytime. Hence, soil HONO emissions in the identified hot spot areas (fig. S2) may account for the observed discrepancies between soil emissions of reactive nitrogen estimated with global models by using the Yienger and Levy algorithm and those derived from "top-down" approaches by using nitrogen dioxide (NO_2) columns measured by satellites over arid ecosystems (*20*, *21*).

Biogenic NO emissions are known to depend strongly on soil temperature (*22*). We measured the temperature dependency of F_N(HONO) and

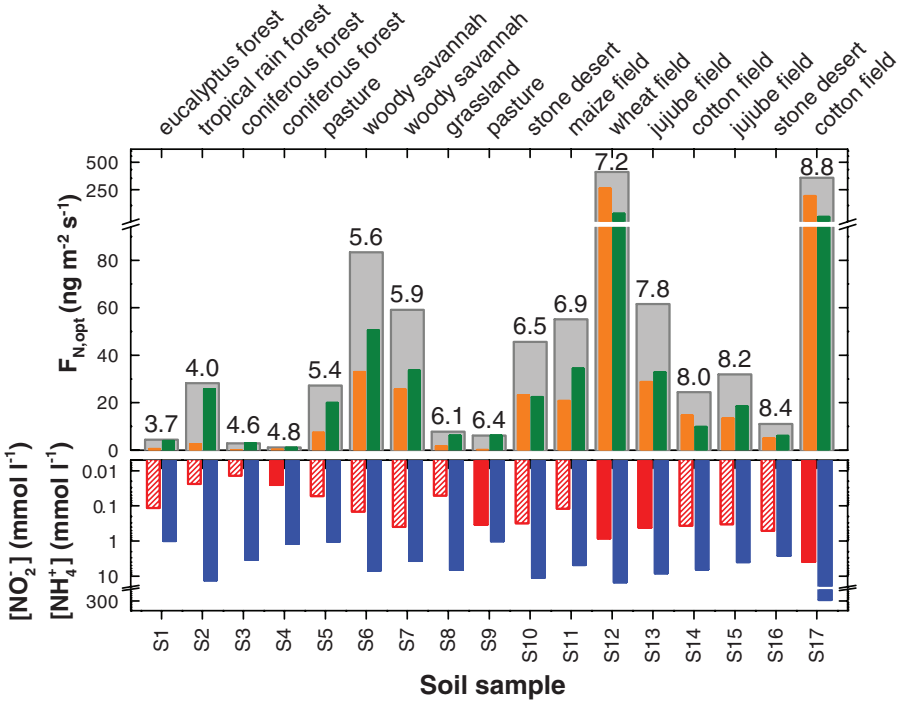


Fig. 2. Optimum emission fluxes of HONO are comparable with those of NO and are largest for NO_2^- rich, neutral-to-basic soils in arid and arable regions. (**Top**) Optimum emission fluxes of HONO (orange bars), NO (green bars), and their sum (gray bars) in terms of nitrogen for each soil sample (at 25°C), arranged by increasing pH. Numbers on top of gray bars represent the soil pH. Land use of soil samples is shown on the top axis. (**Bottom**) Calculated concentrations of NH_4^+ (blue bars) and NO_2^- (red bars) in the soil solution at $F_{N,opt}$(HONO) [striped bars refer to theoretical NO_2^- values at the limit of detection (*10*)].

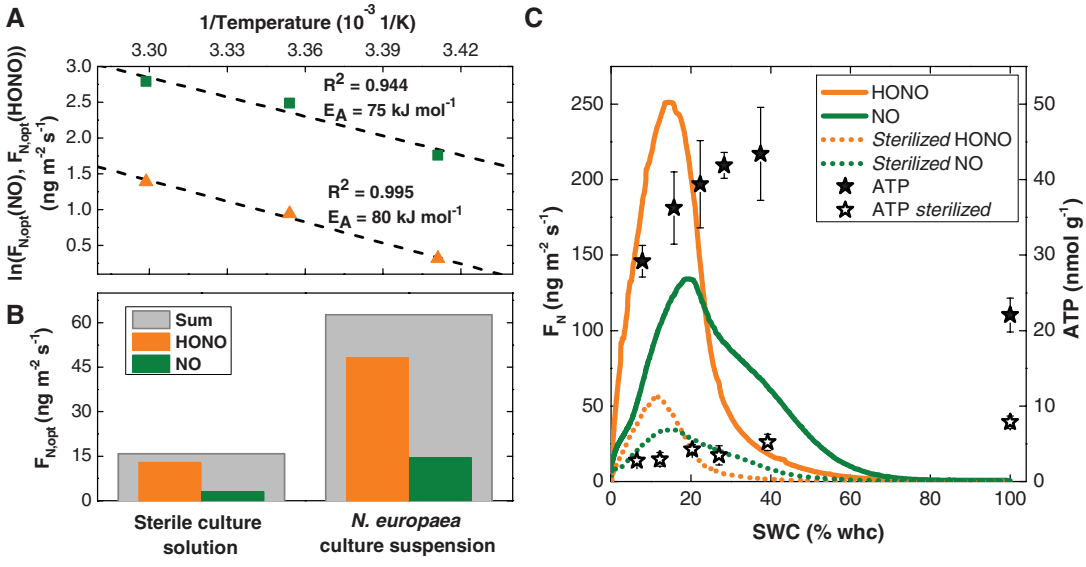


Fig. 3. Ammonia-oxidizing bacteria directly release HONO and cause high emissions from soil. (**A**) Arrhenius plot of the optimum fluxes of HONO (triangles) and NO (squares) for soil sample S8. (**B**) Optimum fluxes of HONO, NO, and their sum for a sterile AOB nutrient solution and a *N. europaea* culture suspension (activity equivalent to $1.1 \cdot 10^{-3}$ nmol ATP l^{-1}) applied to glass beads as a soil proxy. (**C**) Influence of bacterial activity on HONO and NO emissions for soil sample S12. Fluxes of HONO and NO for the untreated soil (solid orange and green line, respectively) and for a sterilized subsample (dotted orange and green line, respectively). ATP concentrations serve as indicators for bacterial activity during the dry-out of the untreated sample (black filled stars) and the sterilized sample (black open stars). Error bars denote SDs of three replicates.

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F_N(NO) from soil sample S8 (an example for HONO is provided in fig. S3). A temperature increase from 20 to 30°C yielded Q_{10} values (averaged over the whole SWC range) of 3.7 (±1.4) for HONO and 2.1 (±0.2) for NO, which is typical for soil respiratory systems (*16*, *23*, *24*). From an Arrhenius plot (Fig. 3A), we obtained similar activation energies for HONO (80 kJ mol^{-1}) and for NO (75 kJ mol^{-1}). These values are much lower than the activation energies reported for denitrification (202 to 250 kJ mol^{-1}) (*25*) but are within the range reported for nitrification by ammonia-oxidizing bacteria (AOB) (25 to 149 kJ mol^{-1}) (*3*, *25*), suggesting that the latter process governs the observed co-emission of HONO and NO.

To test this hypothesis, we investigated a pure culture of *Nitrosomonas europaea*, a common and well-studied AOB (*26*). A suspension of the pure culture (buffered at pH = 8.2) was applied to glass beads serving as an inert soil-like matrix (*16*), and the model system was treated like a soil sample (*10*). $F_{N,opt}$(HONO) and $F_{N,opt}$(NO) of the *N. europaea* culture suspension are compared in Fig. 3B with the emissions by using a sterile AOB nutrient solution additionally containing 0.14 mmol l^{-1} NO_2^-, which equals 0.5 mg kg^{-1} of NO_2^- (in terms of N) in soil. The NO_2^- added to the sterile solution equals the NO_2^- that would have been produced by the bacteria during the experiment and reflects the chemical contribution to the HONO emission from the model system, whereas the observed difference in $F_{N,opt}$(HONO) between the sterile solution and the culture suspension can be attributed to the direct emissions by the AOB. The *N. europaea* culture emits four times more HONO than does the sterile reference, demonstrating that AOB can indeed act as a strong direct source of HONO.

Measured adenosine 5′-triphosphate (ATP) concentrations during the dry-out of S12 (Fig. 3C) show that soil microbes are active also under relatively dry conditions (% WHC < 20%), where $F_{N,opt}$(HONO) is observed. Because ATP is an indicator for microbial activity in general, the maximum activity of AOB might not coincide with the maximal ATP concentration. We applied methyl iodide—a strong sterilization agent for soil (*27*) also targeting nitrification (*28*)—to a subsample of S12 (Fig. 3C). Both HONO and NO emission fluxes were reduced by ~75%, revealing a strong microbial source. This demonstrates that the findings from the model system shown in Fig. 3B are transferable to a real soil sample. The residual emissions can largely be attributed to the chemical source because the ATP content and, hence, the microbial activity was reduced by ~92% at the HONO emission optimum. These results explain the high HONO emissions from nonacidic soil samples.

The conceptual model in Fig. 4 shows that $F_{N,opt}$(HONO) and $F_{N,opt}$(NO) occur in the lower SWC range (~0 to 40% WHC) (*16*, *29*), whereas at high SWC (~40 to 80% WHC), nitrogen is released from soil mainly as the greenhouse gas N_2O. In general, substrate diffusion is limited at low SWC, and gas diffusion is limited at higher SWC (*30*). HONO is produced and emitted during nitrification, which predominates at low SWC (*5*). Samples from different soil and land-use types show their maximal release of the respective nitrogen compound at different optimum SWC (*15*). The magnitude of the maximal emission of each compound varies depending on, for example, nutrient availability and abundance of soil bacteria.

HONO emissions by AOB and possibly other types of bacteria represent an additional component for gaseous losses from the soil nitrogen pool to the atmosphere. Our survey of soils from different ecosystems indicates that HONO emissions may account for up to 50% of the reactive nitrogen release from soil. This contribution of soil HONO emissions is currently not considered in model estimates of global soil reactive nitrogen emissions (*1*) and may constitute one of the major uncertainties in this budget. Furthermore, these HONO emissions contribute to atmospheric chemistry by enhancing the oxidation capacity of the lower atmosphere.

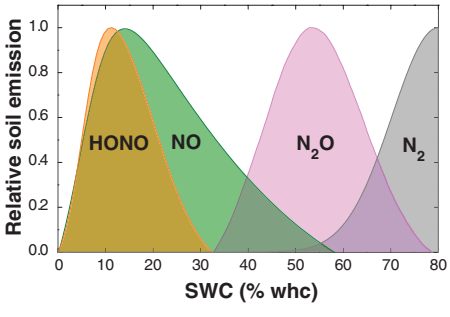


Fig. 4. HONO is a major component of nitrogen emissions from soil. The conceptual model of soil nitrogen emissions as a function of SWC was adopted from Firestone and Davidson (*31*). The curves are based on measurements of HONO, NO, and N_2O emissions from soil sample S12 [N_2 emissions were fitted from (*31*)].

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Supplementary Material

www.sciencemag.org/cgi/content/full/341/6151/1233/DC1
Materials and Methods
Supplementary Text
Figs. S1 to S3
Table S1
References (*32*–*48*)

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Channelized Ice Melting in the Ocean Boundary Layer Beneath Pine Island Glacier, Antarctica

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Ice shelves play a key role in the mass balance of the Antarctic ice sheets by buttressing their seaward-flowing outlet glaciers; however, they are exposed to the underlying ocean and may weaken if ocean thermal forcing increases. An expedition to the ice shelf of the remote Pine Island Glacier, a major outlet of the West Antarctic Ice Sheet that has rapidly thinned and accelerated in recent decades, has been completed. Observations from geophysical surveys and long-term oceanographic instruments deployed down bore holes into the ocean cavity reveal a buoyancy-driven boundary layer within a basal channel that melts the channel apex by 0.06 meter per day, with near-zero melt rates along the flanks of the channel. A complex pattern of such channels is visible throughout the Pine Island Glacier shelf.

In a state of equilibrium, the Antarctic Ice Sheet loses mass through the melting and calving of its outlet glaciers at the same rate as it gains mass through the accumulation of snowfall. Ice shelves, the floating portions of outlet glaciers, provide a control on this equilibrium through a buttressing effect, in which the lateral friction of the ice shelf side walls impedes ice flow, allowing additional ice mass to accumulate upstream of the ice shelf. If ice shelves melt rapidly or break away, equilibrium is lost, ice flow accelerates, and ice sheets experience a net mass loss.

Currently, ice loss from the Amundsen Sea sector of the West Antarctic Ice Sheet (WAIS) contributes ~7% of the global sea-level rise. The WAIS is potentially dynamically unstable, with a capacity to raise global sea level by several meters (*1*). Pine Island Glacier (PIG) is a principal outlet of the WAIS that has rapidly thinned, retreated, and accelerated (*2*–*6*). The spatial pattern of thinning suggests that the glacier drawdown is the direct result of increased basal melting of the ice shelf that has reduced its buttressing effect. The restraint offered by the PIG ice shelf is dependent on its basal melt rate, which in turn is controlled by heat transport in the underlying ocean cavity. Therefore, how an ice shelf interacts with the ocean and melts now and into the future can alter the mass discharge from the Antarctic Ice Sheet in general and the WAIS in particular, affecting global sea level.

The inaccessibility of ice shelf ocean cavities, which are overlain by glacial ice hundreds of meters thick, and the Amundsen Sea ice shelves, which are thousands of kilometers distant from established Antarctic research stations, has severely limited attempts to directly observe ice shelf/ocean interactions in this sector. Successful icebreaker cruises into Pine Island Bay in 1994 and 2009 surveyed hydrography and deployed long-term moorings along the PIG terminus (*7*, *8*). The 2009 cruise included six runs of the unmanned submersible Autosub under the shelf (*9*). These data sets show relatively warm Circumpolar Deep Water (CDW) intruding up onto the continental shelf to the PIG terminus, and 30 km into the ocean cavity. Between 1994 and 2009, the water column became warmer and saltier, and meltwater volume estimates increased by 50%, driven primarily by increased circulation rather than increased heat content (*8*). For 2009, the hydrography-based estimate of mean shelfwide basal melt rate was 33 m year^{-1} (*8*)

The Autosub missions and a dense airborne ice-penetrating radar survey (*10*) have characterized aspects of the ice shelf morphology and ocean cavity bathymetry. Autosub altimeter data revealed a 300-m-high, 700-m-deep transverse ridge that effectively splits the ocean cavity into inner and outer cavities. The airborne radar sections revealed

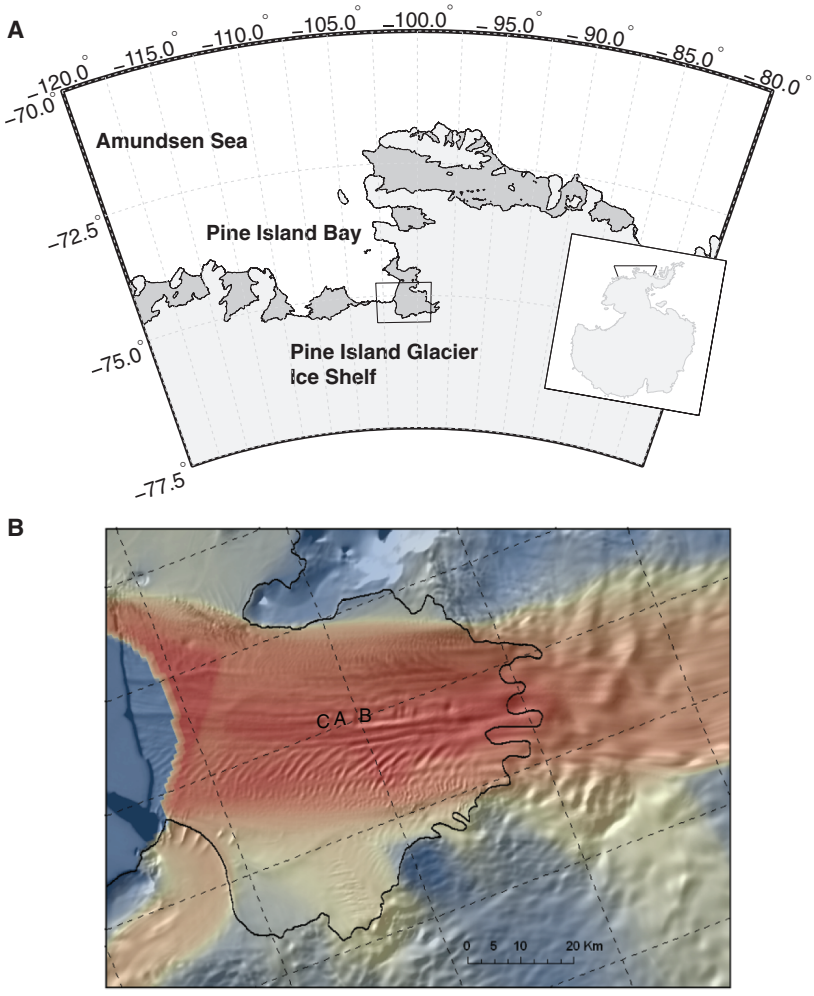


Fig. 1. Locations of the 2012/2013 Pine Island Ice Shelf drill camps. (**A**) Map showing the Amundsen Sea and Pine Island Bay. Light gray is the continental ice sheet; darker gray shows ice shelf areas. The inset map in the lower right shows the entire Antarctic continent, and the smaller box in the lower center shows the PIG area, expanded on in (B). (**B**) A composite of surface satellite imagery (*15*) overlaid with satellite-derived ice surface velocity (*16*) with blue indicating 0 m s^{-1} and red indicating 4000 m s^{-1}. An estimate of the grounding line location is shown as a black line (*17*). The three drill camp locations are shown as A, B, and C.

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a network of longitudinal subshelf channels 0.5 to 3 km wide, with basal crevassing confined to the center of the channels. Extensive surface crevassing was observed along the tops of each of these ridges, indicating lateral tension driven by local hydrostatic imbalance between adjacent ridges and troughs (*11*).

Here we report on a dynamical view of basal melting and the ocean boundary layer below PIG, obtained from surface geophysical surveys and in situ observations within one of the PIG subshelf channel systems. To obtain these observations a (relatively) lightweight hot-water drilling rig, that could be transported by light aircraft and snow machines, was used to make 20-cm-diameter holes through the 400- to 500-m-thick ice shelf. A specialized suite of ocean instrumentation was developed that could fit down the narrow holes, sample turbulence and lateral transport rates in the ocean cavity, and autonomously offer two-way communication of data and sampling commands over year-long sampling periods. These detailed observations are required to understand the physical processes in the ocean cavity, and their variability, that control basal melting.

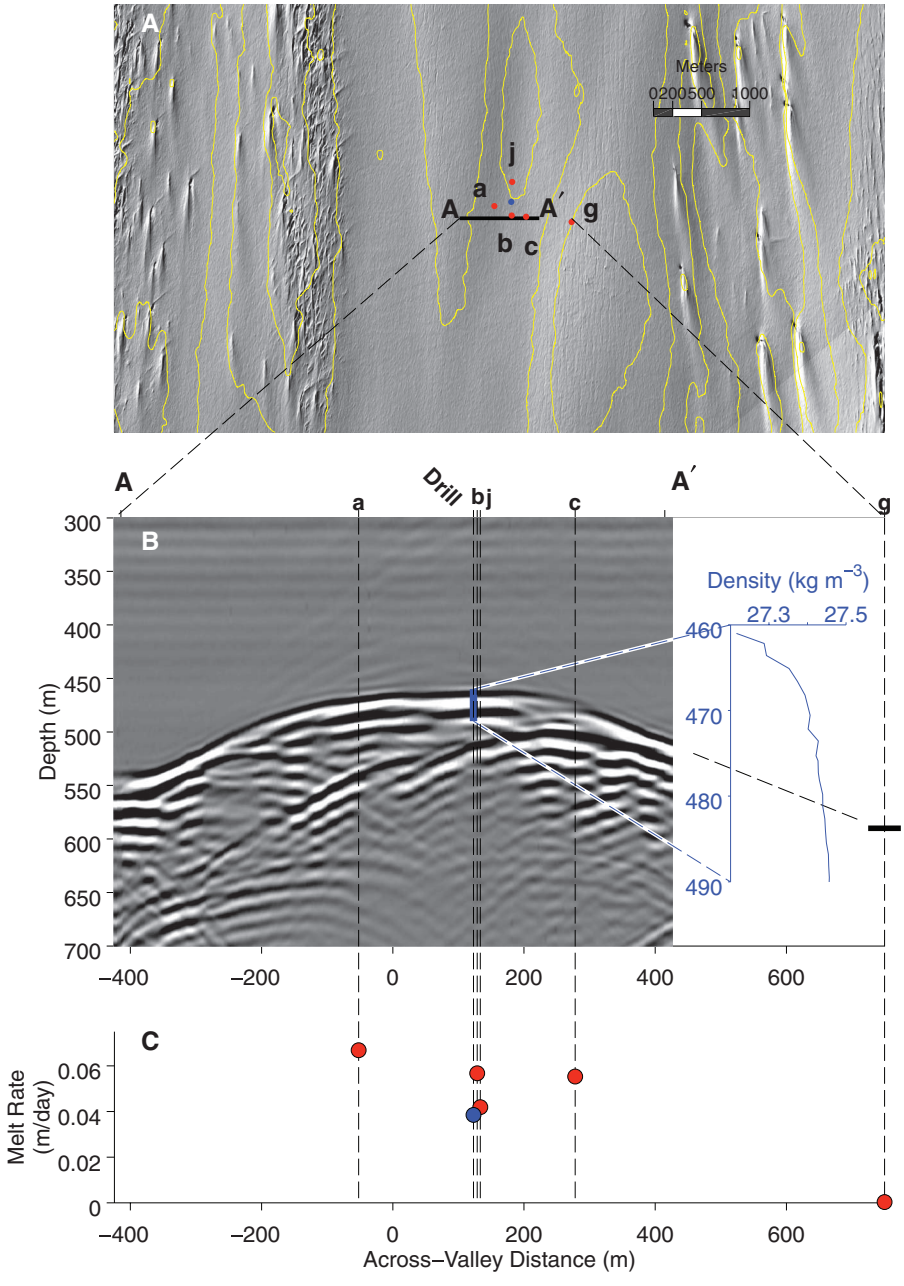


Fig. 2. Ice shelf surface and basal structure, and basal melt rates. (**A**) 1-m-resolution visible satellite image of the area around drill A with a 5-MHz ice-penetrating radar transect shown as the A–A′ line. pRES sites are a, b, c, j, and g. (**B**) An upstream-looking channel cross-section from the radar transect. The ice bottom is visible from 450 to 550 m, referenced from the ice surface. A CTD density anomaly profile between 460 and 490 m shown on the right indicates the structure 30 m down through the buoyant ocean boundary layer plume. (**C**) pRES melt rates for the five locations in (**A**) are shown as red dots, with the scale in red on the right. The blue bar and dot represent 35-day mean melt rates from the flux package altimeter deployed from the bore hole.

Three drilling camps (Drill A, B, and C) were established on the PIG shelf during December 2012 and January 2013 to access the ocean cavity. The camps were positioned in the center of the shelf, away from the heavily crevassed side shear zones (Fig. 1B) and within an approximately 1-km transverse wavelength valley and ridge system observed in previous airborne radar surveys (*10*) (Fig. 2A). This shallow, snowdrift-covered valley is flanked by crevassed ridges, with ridge-to-valley surface elevation changes on the order of 10 m (*O*). Drills A and C were seaward of the transverse seafloor ridge, and Drill B was located on the up-glacier side of the ridge. Here we focus on Drill A observations.

An 850-m-long across-valley transect was made with low-frequency radar (Fig. 2A). Basal melt rates near the radar transect line were measured using a phase-coherent radar (pRES) at five sites (referred to as pRES a, b, j, c, and g; see methods in the supplementary materials). The drilling of a 450-m-deep hole through the ice shelf permitted a full water column conductivity-temperature-depth (CTD) cast and the deployment of a long-term, fixed-depth "flux package." The flux package, initially deployed with its sample volume 2.3 m below the ice, tracks the ice/ocean interface with an altimeter and measures ocean velocity, temperature, and salinity at a sufficiently fast rate (4 Hz) to calculate vertical turbulent fluxes of momentum, heat, and salt.

The radar echogram (Fig. 2B) shows a 600-m-wide, smooth-sided basal channel, with ice shelf thickness on the underside of the shelf decreasing from 540 m on the channel banks to 460 m near the center. At pRES b and j, melt rates of 0.0570 ± 0.0003 m day^{-1} and 0.0420 ± 0.0003 m day^{-1} were determined from continuous time series of length 29.4 and 14.6 hours. At pRES a and c, melt rates of 0.067 m day^{-1} and 0.055 m day^{-1} were calculated by reoccupying the sites at 11- and 13-day intervals, respectively. At pRES g, on the channel bank, basal melting was <0.001 m day^{-1}, near the resolution limit of the system (Fig. 2B). Flux package acoustic backscatter profiles precisely track the ice/ocean interface (Fig. 3A). Melting within the *O* (5 cm) altimeter footprint (Fig. 3B) is fairly steady, with a linear fit from day 5 to 35 yielding a rate of 0.039 m day^{-1}. The altimeter melt rate is nearly equal to the adjacent pRES j rate, whereas it is 30% less than the pRES b rate, located 80 m upstream from the drill hole. Taken together, the melt rate estimates show that, at Drill A, there is rapid, spatially uniform, and steady basal melting within the channel and minimal melting outside of the channel (Fig. 2C).

Time series of Reynolds-averaged ocean properties show that the channel boundary layer was relatively warm and fresh and steady over the month when these observations were collected.

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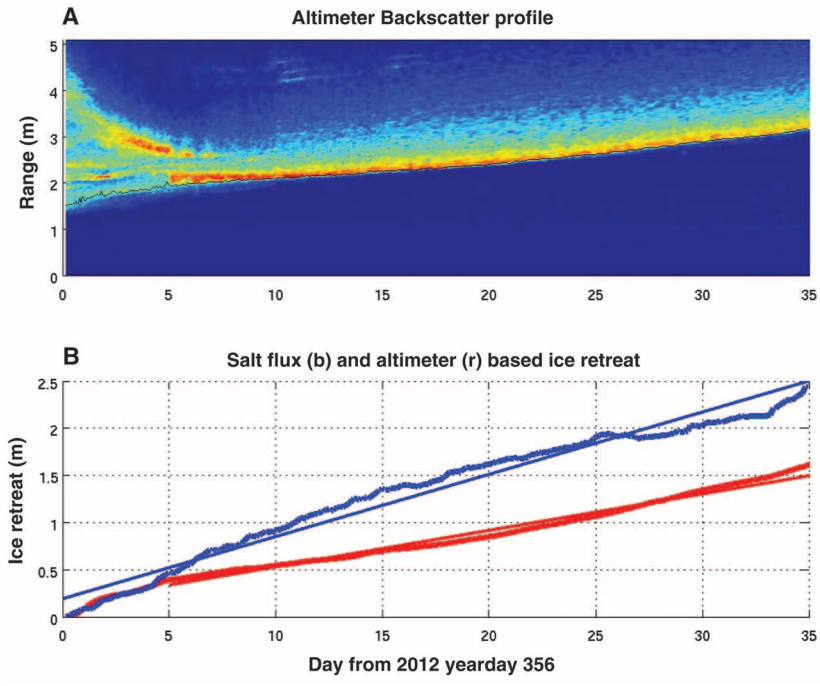


Fig. 3. Time series of the ocean/ice interface retreat. (**A**) 35-day time series starting at 22 December 2012 of acoustic backscatter strength from an upward-directed altimeter on the fixed-position flux package. The blue-to-red color scale represents a five order of magnitude change in backscatter strength. The derived ice/ocean interface is traced as a thin black line. (**B**) The thick red line represents the backscatter-inferred interface, whereas the thinner red line is a linear fit from days 5 to 35. The thick blue line is an ice retreat estimated from temporally integrated turbulent salt fluxes measured by the flux package, whereas the thin blue line is the corresponding linear fit to this retreat rate.

Mean current speed (Fig. 4A) increased uniformly from 0.11 to 0.15 m s^{-1}, whereas the mean current direction was consistently seaward, along the channel axis (not shown in Fig. 4). There were no tidal or other distinct oscillatory motions in the boundary layer fluctuations over the 35-day period considered here. Departure from freezing increased uniformly from 1.35 to 1.42 K (Fig. 4C). Most likely, these gradual changes in measured mean current speed and temperature are the result of vertical gradients within the strongly sheared boundary layer moving past the sensors as the ice/ocean interface slowly receded. Near-interface salinity was 33.85 practical salinity units (psu), which is fresher than the 34.1-psu surface waters observed in terminus surface waters in 2009 (*7*). The turbulent shear stress was steady, with a mean friction speed of 0.0086 m s^{-1} (Fig. 4B, methods, and eq. S1). Vertical salt fluxes were variable, including negative values, with a 35-day mean value of 2.8×10^6 psu m s^{-1}. Positive salt fluxes represent downward turbulent fluxes of fresh water from melting at the ice shelf base.

Integration of the vertical salinity flux provides a history of interface retreat (Fig. 3B, methods, and eq. S2) that is an areal average of upstream melting and so is potentially more representative than the altimeter-based estimate. The average melt rate inferred from the salt flux is 0.066 m day^{-1}. This flux-based melt rate estimate agrees well with the pRES and altimeter estimates, connecting the basal melting of the ice shelf to turbulence in the channelized ocean boundary layer.

The CTD density profile (Fig. 2B) shows that the boundary layer is thin (12 m) and buoyant. The basic dynamics of the layer were examined by testing a simplified, vertically integrated momentum balance (*12*), in which the buoyancy force

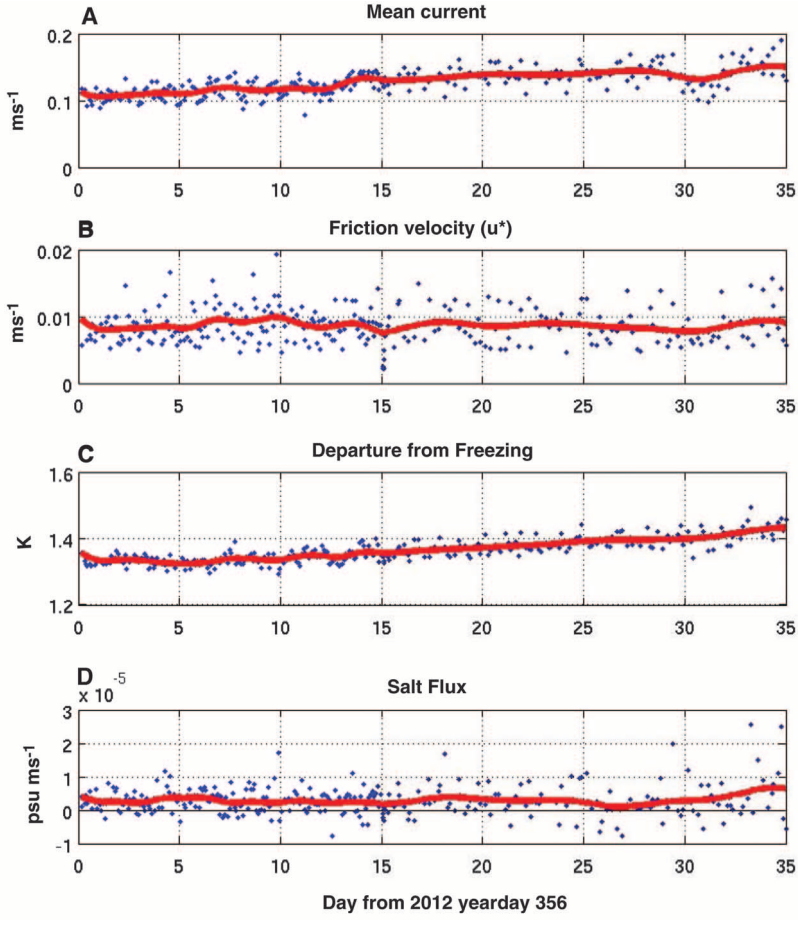


Fig. 4. Time series of ocean boundary layer properties. A corresponding time series of mean current (**A**), turbulent friction velocity (**B**), the departure from freezing $T_d = T - T_{fp}$ (T, in situ temperature; fp, the pressure- and salinity-dependent local freezing point) (**C**), and turbulent vertical salt flux (**D**) from the fixed position turbulent flux package at Drill A with the same time axis as Fig. 3. The thick red lines represent 2-day-period low-pass filtered versions of each time series.

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arising from the vertical density gradient and the sloping interface

$$\alpha g \int_0^{\delta} (\rho - \rho_\delta) dz \quad (1)$$

is balanced by the turbulent shear stress at the interface. With density ρ and layer height δ taken from the CTD profile and basal slope α calculated from depth differences between Drill A and B, the buoyancy force is estimated at 0.043 Pa. This compares favorably to the average shear stress measured by the flux package, $\rho u_*^2 =$ 0.076 Pa (Fig. 4B), indicating that the observed boundary layer flow is forced by the melt-generated buoyancy acting along the sloping base of the shelf.

These in situ measurements of the underside of the PIG ice shelf reveal strong but spatially non-uniform ice/ocean interaction, in which ocean boundary layers are strongly coupled to basal melting: They are buoyantly forced by melt water and are constrained by the resulting melt channel morphology. The pRES melt rate estimates document the cross-channel variability in melt rate that results from the channelized flow, whereas the longer-term flux package estimates demonstrate that melt rates and boundary layer properties were fairly steady over the month of observations, which is consistent with the idea that the forcing is due to the relatively slowly evolving buoyancy field within the ocean cavity. If these direct melt rates within the channel are annualized, they range between 14.2 and 24.5 m $year^{-1}$. However, we expect that melt rates will be affected by seasonal or other long–time-scale variability associated with the oceanic forcing. We also expect along-shelf spatial variability in cross-shelf melt patterns, as supported by recent altimetry analyses (*13*) that infer preferential melting of keels toward the terminus. The continuity of the channels seen in satellite imagery and the airborne radar survey, in conjunction with the vigorous melt rates here described, indicate that basal melting is active from the grounding line to at least the mid-shelf location of the observations. In addition to our observations, a recent idealized numerical simulation of an ice shelf base and ocean boundary layer has suggested that channelization is of fundamental importance, because a channelized base actually melts much less vigorously than a nonchannelized one (*14*). The remarkable ice/ocean coupling evident in our observations points to the need to represent channelized ice/ocean interaction in models of PIG and similar outlet glaciers in global climate simulations of sea-level change.

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Supplementary Materials

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Materials and Methods
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Marine Taxa Track Local Climate Velocities

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Organisms are expected to adapt or move in response to climate change, but observed distribution shifts span a wide range of directions and rates. Explanations often emphasize biological distinctions among species, but general mechanisms have been elusive. We tested an alternative hypothesis: that differences in climate velocity—the rate and direction that climate shifts across the landscape—can explain observed species shifts. We compiled a database of coastal surveys around North America from 1968 to 2011, sampling 128 million individuals across 360 marine taxa. Climate velocity explained the magnitude and direction of shifts in latitude and depth much more effectively than did species characteristics. Our results demonstrate that marine species shift at different rates and directions because they closely track the complex mosaic of local climate velocities.

Global warming during the past century has had many biological effects, including changes in phenology and poleward shifts in species distributions (*1*–*3*). However, species have not responded uniformly, and shifts in their distributions have occurred at widely different rates and in different directions (*1*–*10*). In both marine and terrestrial assemblages, up to 60% of species are not shifting as expected; i.e., to higher latitudes, higher elevations, or greater depths (*1*–*10*). A range of hypotheses has been proposed to explain this observed variation, including the effects of habitats (*11*), species interactions (*11*, *12*), sensitivity to environmental gradients (*13*), response times (*10*), colonization abilities (*14*), and physiological or evolutionary adaptations (*15*). In essence, many of the leading hypotheses have emphasized biological differences among species (*8*–*10*, *14*).

An alternative and possibly more general hypothesis posits that local differences in climate velocity (*16*, *17*) can explain heterogeneity in species shifts. Climate velocity is the rate and direction that isotherms shift through space, and it combines both temporal and spatial rates of temperature change (*16*, *17*). Previous authors have hypothesized that species may follow

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climate velocities (*16*–*19*), but a direct test has not been attempted (*2*, *13*, *18*). An examination of broad taxonomic groups found faster shifts in regions of higher climate velocities but did not examine variation among species or shifts toward lower latitudes (*2*). These issues are particularly important in the ocean, where climate velocities are up to seven times higher than on land (*16*, *18*).

To understand how marine species respond to climate velocity, we compiled four decades of scientific surveys of fish and invertebrates from the continental shelves of North America across nine regions spanning ~3.3 million km^2 and 60,394 bottom-trawl samples from 1968 to 2011 (fig. S1 and table S1). These surveys captured 128 million organisms from 580 populations of 360 species or species groups; we refer to these collectively as "taxa."

We measured range shifts by tracking the location of range centroids (*20*). Taxa showed considerable variation in the direction and rate of shifts, both within regions (Fig. 1, B to D) and between regions (Fig. 1A and figs. S2 to S4). Individual species shifted north (for example, American lobster in the northeast), south (big skate on the west coast), or remained approximately stable (Pacific cod in Alaska, Fig. 1). Defining an assemblage as the set of sampled taxa within a geographic region, four assemblages shifted poleward (Fig. 1, A, B, and D), whereas five shifted south (Fig. 1, A and C, and fig. S2). For example, assemblages from the west coast and the Gulf of Alaska shifted south at >11 km/decade during a cooling period that is thought to reflect multidecadal climate variability (*21*).

At the assemblage level, regional temperature changes explained differences in observed shifts, although modified by geographic constraints. Assemblage shifts were positively but weakly related to bottom temperature trends (r^2 = 0.27, P = 0.15, n = 9 regions; Fig. 2A). However, the Gulf of Mexico assemblage (Fig. 1C) was an outlier in this relationship and the only warming region with an east-west coastline that prevented poleward shifts. Instead, this assemblage shifted deeper (Fig. 2D). After this region was omitted, bottom temperature explained more than half of the variation in assemblage shifts (r^2 = 0.60, P = 0.023, n = 8 regions). Surface temperature trends were not correlated to latitudinal shifts (P = 0.75, r^2 = 0.02; without the Gulf of Mexico, P = 0.53, r^2 = 0.08). However, assemblages that experienced increasing surface temperatures tended to shift deeper, away from warming waters (r^2 = 0.80, P = 0.0028, n = 8 regions; Fig. 2D and fig. S5). Depth shifts were not related to bottom temperature changes (r^2 = 0.12, P = 0.36). These relationships concern whole assemblages, not individual taxa. Individual shifts were weakly correlated to changes in average regional temperature (latitude versus bottom temperature without the Gulf of Mexico: P = 0.0013, r^2 = 0.022, n = 474 taxa; depth versus surface temperature: P < 0.0001, r^2 = 0.05, n = 497 taxa).

Although regional patterns can be informative, they do not reveal the extent to which individual taxa follow local variation in climate velocities. Climate velocities are often calculated for grid cells (*16*, *17*), but taxon distributions are irregular and a taxon-specific version of climate velocity is needed that averages velocities across species' ranges. We therefore used survey data

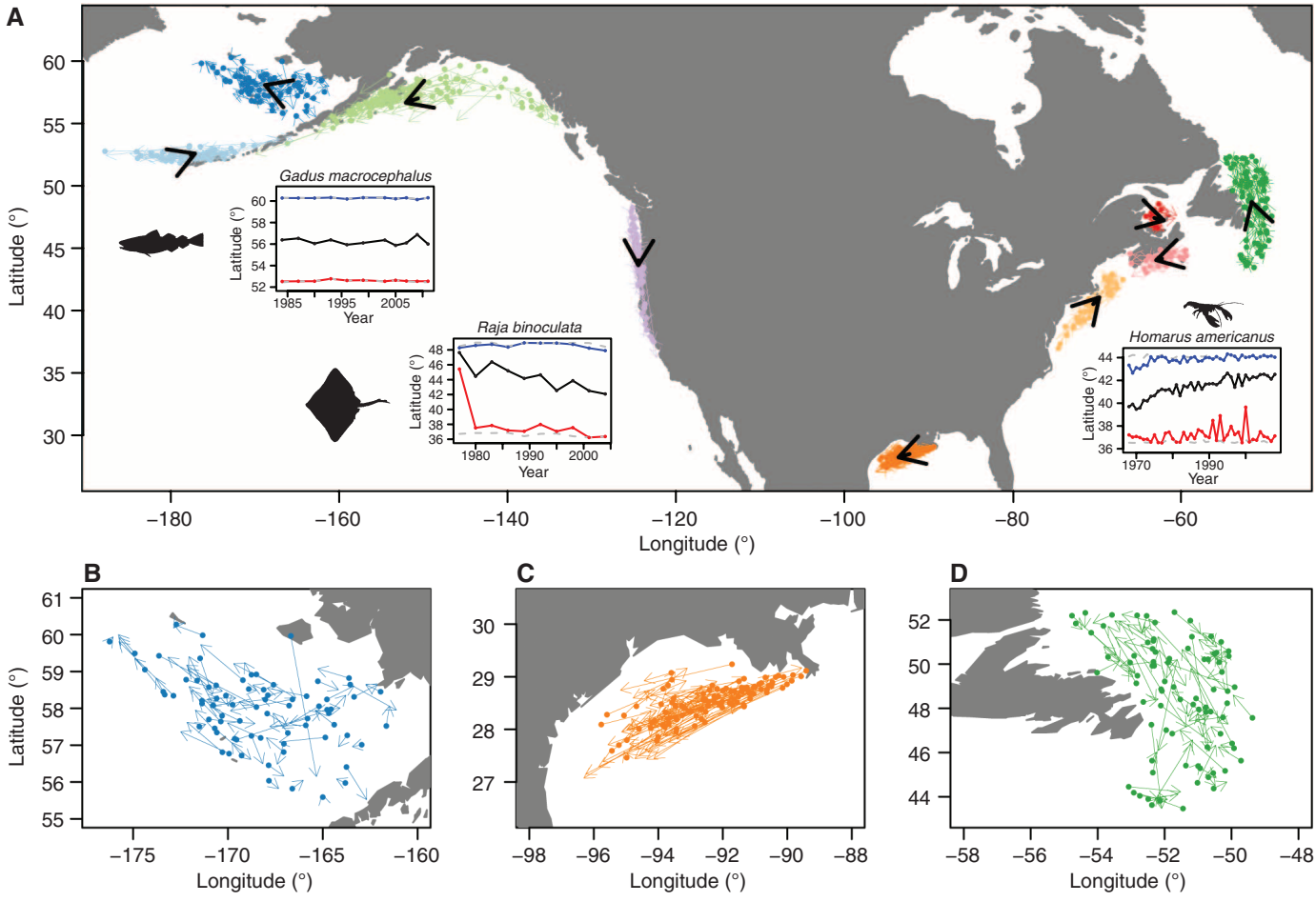


Fig. 1. Shifts in the distribution of marine taxa. (**A**) Vectors show the average shift in latitude and longitude for each taxon (colors) and the mean shift in each region (black). Insets show the mean (black), maximum (blue), and minimum (red) latitude of detection for Pacific cod (*Gadus macrocephalus*) in the Gulf of Alaska, big skate (*Raja binoculata*) on the U.S. West Coast, and American lobster (*Homarus americanus*) in the Northeast. Gray dashed lines in insets indicate the range of surveyed latitudes. Detailed views are also shown of (**B**) the Eastern Bering Sea, (**C**) the Gulf of Mexico, and (**D**) Newfoundland.

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to calculate the temperature range inhabited by each taxon and measured taxon-specific climate velocity as the rate and direction that these temperatures shifted across the landscape (*20*). We found considerable spatial variation in climate velocities (Fig. 3). The taxa also showed considerable heterogeneity: 46% shifted south and 58% shifted shallower (Figs. 1 and 3 and figs. S5 and S6).

Such heterogeneity among taxa, however, was not random. Instead, differences in climate velocity explained much of the variation in the rate and direction of latitudinal range shifts ($r^2 = 0.38$, $P < 0.0001$, $n = 325$ taxa; Fig. 3A). The relationship remained significant if random effects for region were included ($P < 0.0001$) or if we used bootstrap resampling to generate a null distribution of correlations ($P = 0.019$) (*20*). Across all taxa, 74% shifted latitude in the same direction as climate velocity, and 70% shifted depth in the same direction. This explanatory power was equally high for "non-intuitive" shifts that deviate from the poleward-and-deeper pattern: 73% of shifts to lower latitudes and 75% of shifts toward shallower water were explained by climate velocity.

To estimate whether taxa were shifting faster or slower than climate velocity, we measured the bias [in degrees north (°N) per year] as well as relative bias between taxon-specific velocities and observations (*20*). However, we found that taxa on average do not lag (bias: $P = 0.13$, mean = 0.003 °N/year; relative bias: $P = 0.39$, mean = 4.68).

Climate velocity can also be projected across depth, and we found evidence that climate velocities can explain variation in the rate and direction that taxa shifted shallower or deeper ($r^2 = 0.13$, $P < 0.0001$, $n = 325$ taxa; Fig. 3B and fig. S7). Depth biases were not significantly different from zero (bias: $P = 0.60$, mean = −0.040 m/year; relative bias: $P = 0.49$, mean = 3.8), again indicating little to no lag in species response to changing climate.

There was little evidence that other factors could explain variation in the speed and direction of taxon shifts. For example, adding survey and species characteristics to a multiple regression model only increased the explained variance in species shifts for all taxa from 38% (model with climate velocity as the only explanatory variable) to 42% (full model with all variables), or from 36 to 45% for fish (Table 1 and table S5). Survey and species characteristics, however, may be more likely to influence the speed (absolute value of °N/year) rather than the combined speed and direction of observed shifts. Higher relative variable importance (RVI) for survey extent and duration, as well as for climate velocity (table S4), suggested that the most rapidly shifting species might not appear in our analysis because they left the survey area. There was also limited evidence that invertebrates, commercially fished taxa, pelagic taxa, taxa with declining biomass, fish with small ranges, fish higher in the food chain, and large fish shifted faster (tables S4 and S5). Such species characteristics, however, explained at most 1.3% of the variation in speed across all taxa (3.3% across all fish), as compared to 18% for climate velocity (or 20% across all fish). We conclude that variation in the environment is a much more powerful predictor of taxon shifts than variation in life history.

A previous study also found that species traits had little power to explain distribution shifts, but it did not examine climate velocities (*14*). Likewise, climate heterogeneity has been connected to the direction but not magnitude of shifts in birds and fish (*3*, *5*, *7*, *13*). Recognizing and quantifying heterogeneity in climate velocities across multiple scales may substantially improve our ability to explain ecological changes and project into the future. Our findings suggest that bioclimate envelope methods are valuable (*19*) but can be improved by the use of fine-scale climate data.

Beyond climate velocity, other influences on species shifts probably include species interactions (*12*), fisheries harvest, habitat, and species' abilities to disperse and adapt (*14*, *15*). Release from a poleward-shifting predator, for example,

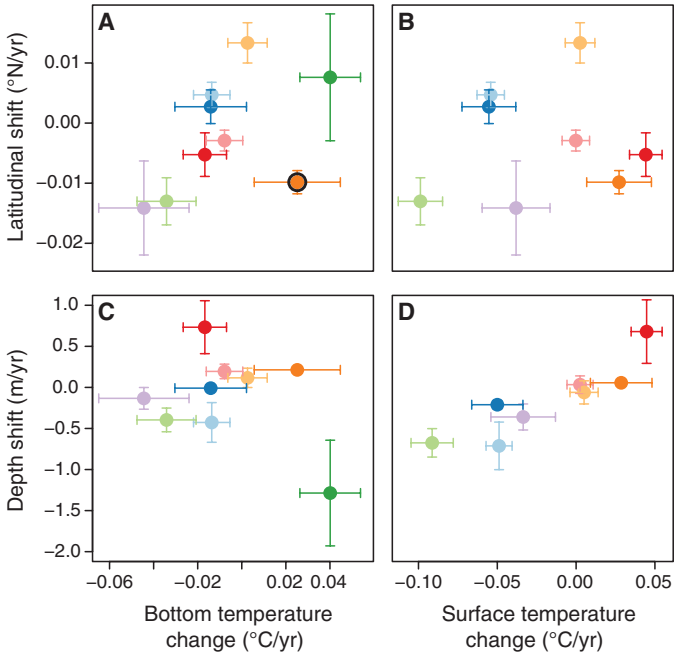


Fig. 2. Relationships between sea temperature change and assemblage shifts. (**A**) Latitude shifts versus bottom temperature (the black circle marks the Gulf of Mexico), (**B**) latitude shifts versus surface temperature, (**C**) depth shifts and bottom temperature, and (**D**) depth shifts and surface temperature. Positive depth shifts are toward deeper water. Error bars show standard errors, and colors match the taxon vectors in Fig. 1.

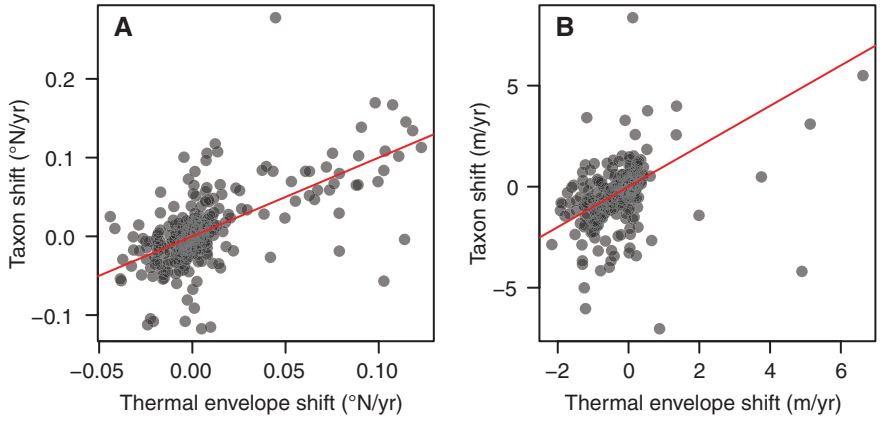


Fig. 3. Climate velocity and taxon shifts. The relationship between taxon-specific climate velocities and observed shifts in taxon range centroids is shown for (**A**) shifts in latitude and (**B**) shifts in depth. The 1:1 line is shown in red.

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Table 1. Models explaining the direction and speed (°N/year) of latitudinal shifts in taxon distributions. Models were fit to data either for all taxa (top section, $n = 325$ taxa) or for fish alone (bottom section, $n = 199$ taxa). RVI ranks all explanatory variables from high to low importance. The model coefficients associated with each variable are shown for the most parsimonious model with the lowest Akaike information criterion (AIC) value (best model); a model with all factors retained (full model); a multimodel average (model average); and models with only climate velocity, only survey characteristics (survey char.), or only species characteristics (species char.) retained as explanatory variables. The ΔAIC indicates the difference in model parsimony as explained by AIC relative to the best model; a ΔAIC value <10 indicates higher support for a model. Values of r^2 and Akaike weight for each model are also shown. RVI and Akaike weights were calculated across all possible models (128 for all taxa, 1024 for fish alone).

Variable	RVI	Best model	Full model	Model average	Climate velocity	Survey char.	Species char.
				All taxa			
Climate velocity	1	0.92	0.87	0.9	0.96		
Survey extent	0.505		0.00093	0.00044		0.005	
Survey duration	0.3		0.00015	1.80×10^{-5}		0.0012	
Fish/invert.	0.796	0.011	0.0098	0.0084			0.02
Unfished/fished	0.848	−0.0087	−0.0085	−0.0079			−0.0099
Pelagic/demersal	0.776	0.016	0.014	0.012			0.024
Biomass trend	0.45		0.0048	0.0023			0.0056
ΔAIC		0	2.52		11.1	127	145
r^2		0.41	0.42		0.38	0.12	0.081
Akaike weight		0.11	0.03		0.00041	3.50×10^{-29}	2.90×10^{-33}
				Fish			
Climate velocity	1	0.76	0.77	0.78	0.93		
Survey extent	0.838	0.0023	0.0017	0.0018		0.0063	
Survey duration	0.42		−0.00041	−0.00021		0.00074	
Growth rate	0.3		−0.0016	−0.00066			−0.0091
Unfished/fished	0.41		−0.0068	−0.0028			−0.0025
Pelagic/demersal	0.947	0.028	0.023	0.025			0.041
Range size	0.286		3.70×10^{-5}	1.30×10^{-5}			0.00013
Biomass trend	0.344		0.0034	0.0013			0.0046
Trophic level	0.356		−0.0061	−0.0022			−0.005
Maximum length	0.956	0.014	0.014	0.014			0.013
ΔAIC		0	8.63		20.4	72.1	95.9
r^2		0.44	0.45		0.36	0.18	0.13
Akaike weight		0.071	0.00095		2.60×10^{-6}	1.50×10^{-17}	1.10×10^{-22}

could drive a prey's range centroid toward lower latitudes. However, even such shifts would be subject to the physiological constraints imposed by thermal conditions.

We find that marine taxa follow climate velocities with surprising accuracy, a pattern that holds largely irrespective of individual life histories. Hence, it appears that much of the seemingly individualistic variation in the magnitude and direction of species range shifts can be explained by local variation in climate velocity. Our results contrast with evidence that terrestrial species lag behind climate velocity (*4*, *10*) [though see (*5*)] and suggest that marine species may be better able to keep pace with climate change. Marine species may shift more rapidly than species on land because they face fewer barriers to dispersal and more completely fill their thermal niches (*6*). However, the observed rapid range shifts will fundamentally reorganize marine communities. Climate-induced movements of highly commercial species have already sparked cross-border fisheries conflicts, and they can confound traditional management approaches (*8*). Forecasts of climate velocity may provide an important tool to anticipate the scale and magnitude of these impacts now and into the future.

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Supplementary Materials

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Materials and Methods
Figs. S1 to S6
Tables S1 to S5
References (*22*–*26*)

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The Molecular Trigger for High-Speed Wing Beats in a Bee

H. Iwamoto* and N. Yagi

The high-frequency wing beat of higher-order insects is driven by self-sustained oscillations of constantly activated flight muscles. However, whether its underlying mechanism is based on flight muscle–specific features or on preexisting contractile functions is unknown. Here, we recorded X-ray diffraction movies, at a rate of 5000 frames/second, simultaneously from the two antagonistic flight muscles of bumblebees during wing beat. Signals that occurred at the right timing for triggering each wing-beat stroke were resolved in both muscles. The signals likely reflect stretch-induced myosin deformation, which would also enhance force in vertebrate muscles. The results suggest that insects use a refined preexisting force-enhancing mechanism for high-frequency wing beat, rather than developing a novel mechanism.

Like vertebrate skeletal and cardiac muscles, insect flight muscles (IFMs) are cross-striated, and their myofibrils consist of sarcomeres connected in series. Also, the contraction and relaxation of IFMs are controlled by the regulatory proteins on the thin filament, troponin and tropomyosin. However, IFMs, especially the variety called asynchronous IFMs, are highly specialized for high-speed oscillation with small amplitudes. Unlike in vertebrate skeletal muscle, the oscillation of IFM does not accompany the release and/or reuptake of intracellular calcium but is caused by the mechanism of stretch activation, or SA (*1*–*3*). SA is observed in many types of muscles (*1*, *4*, *5*) but most conspicuously in asynchronous IFMs. Despite decades of research, the molecular mechanism of SA is still unknown. Although it is easy to reproduce SA by using isolated, demembranated IFM fiber specimens and externally applying a stretch, it is unclear how SA starts to operate in the wing-beat cycle of live insects and how it is timed.

For IFM research, the giant waterbug (*Lethocerus*) (*1*, *3*, *6*–*12*) and the tiny fruit fly (*Drosophila*) (*13*–*15*) have been used most frequently. The medium-sized bumblebee (*Bombus*) is suited for IFM studies in many ways. Its IFM fibers are long enough (3 to 5 mm) to allow mechanics and X-ray diffraction recordings with ease (*11*, *12*, *16*); its thorax is small enough for X-rays to penetrate and produce live diffraction images. Its IFM proteins are biochemically stable. Specimens are readily collected in the wild and are also commercially available.

Live bumblebees, with aluminum tubes glued on top of their thoraces, were placed in an X-ray beam path so that beams would hit them from the side (Fig. 1). In this way, the beams hit both of the antagonistic IFMs (dorsal longitudinal muscle, DLM, and dorsoventral muscle, DVM), and the beam axis was perpendicular to the fiber axes of both muscles (*17*). Two fast CMOS (complementary metal oxide semiconductor) video cameras were driven at 5000 frames/s; one recorded diffraction patterns and the other, the bee itself beating its wings. The images of the bee were used to determine the phase of wing-beat cycles (movie S1). The bees beat their wings at ~120 Hz (single wing-beat cycle, ~8 ms), which corresponds to ~40 X-ray frames per cycle. As the cycle time was variable, the diffraction movies were edited afterward, so that a single cycle consists of exactly 40 frames (figs. S1 and S2).

One of the frames of the X-ray movie taken from a single bee is shown (Fig. 2A) next to a typical diffraction pattern recorded from skinned IFM fibers for comparison (Fig. 2B). Although the patterns of both DLM and DVM overlap, many of their reflections can be observed separately because of the angle difference between the axes of the two muscles (~50° to 60°). Even in these movies from a single bee (movies S2 and S3), the strengthening and weakening and spacing changes are evident in some reflections.

To improve the signal-to-noise ratio and visibility, diffraction patterns from all bees were summed, after reorienting each pattern so that the equator of either of the two muscles is horizontal (Fig. 2, C to F). In the movies created this way (movies S4 and S5), more of the reflections are clearly visible, and they are easily identified by comparison with the pattern from skinned IFM fibers (Fig. 2B).

Besides signals of molecular movements, these movies provide noninvasive estimates of parameters such as sarcomere length and force (although these estimates should be treated with caution; see supplementary text S1). Here, the signals of primary interest are described, and for simplicity, we call them the length, myosin-binding, and force and trigger signals (Fig. 3). Some additional signals are dealt with in fig. S3.

The length signal (the top rows in Fig. 3) refers to the change of sarcomere length, as estimated from the filament lattice spacing, which is inversely related to the sarcomere length under constant-volume conditions. The traces are almost purely sinusoidal (with little harmonic components), as expected, from efficient resonance of the thorax. The DVM is shortest when the wings are upright. The lengths of the DLM and DVM are almost perfectly in antiphase (179.2° phase difference) (table S1).

The myosin-binding signals (second rows) refer to the intensities of three reflection spots (1,0,2; 2,1,1; and 3,1,1). Because of the near-crystalline order of contractile proteins, the layer-line reflections arising from myosin and actin filaments are finely sampled into discrete spots. Here, they are named after their Miller indices (*hkl*), which report the number of strongly bound (rigorlike) myosin heads on actin (*6*) (for detailed explanations of reflections, see supplementary text S1). These signals follow nonlinear, sawtoothlike time courses. After reaching minima around the time of shortest sarcomere length, the signals slowly build up, and this likely represents the commonly observed process of force recovery after a release. Apparently, the increase of the signals is accelerated in the late lengthening phase, probably because the effect of SA to enhance force becomes prominent here. The

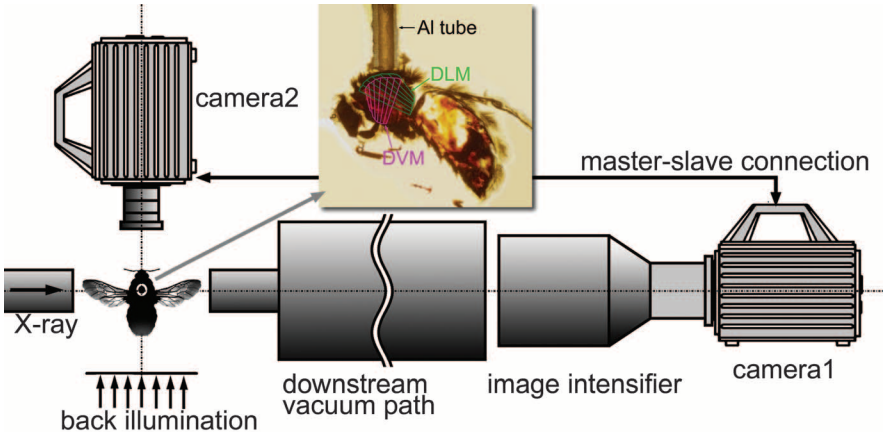


Fig. 1. Experimental setup for X-ray diffraction recordings. See Materials and Methods for details. X-rays were irradiated at points where DLM and DVM overlap each other (inset).

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signals reach their maxima early in the shortening phase and then decrease precipitously, and they have reached their minima by the time of the shortest sarcomere length.

The force signal (third rows) refers to the *d*-spacing of the myosin meridional reflection at ~14.5 nm, whose change reports the elastic extension of the myosin filament (*15*, *18*, *19*). This signal follows a sawtoothlike time course very similar to those for the myosin-binding signals but with a substantial phase lead. That is, it peaks at the onset of shortening and reaches a minimum well before the time of the shortest sarcomere length. This phase lead is explained by two possible mechanisms: Force per attached myosin is greater during lengthening and smaller during shortening. The other is the contribution of viscoelastic drag (*10*). The sarcomere keeps shortening after the force reaches its minimum, and this may occur in a resonating system where inertial moment is involved.

Finally, the trigger signal, as we tentatively call it (bottom row), refers to the 1,1,1 reflection spot. This signal has been counted as one of the reflections that report strong myosin binding (*6*), but its time course of change is very different from those of other spots. In DLM, its phase is well ahead of those of myosin-binding signals, and in DVM, this tendency is even more pronounced so that its time course is reverse-sawtooth–shaped. Its phase lead over the myosin-binding signals is greater than 20° in terms of fundamental component (table S1). The fastest rise of the signal occurs during the lengthening phase, which suggests that it is elicited by stretch. Actually, this is the first reflection to respond to the stretching of skinned IFM fiber preparations (*20*).

The rise of the 1,1,1 signal is accompanied by a fall of the 2,0,1 signal. Model calculations show that these reciprocal intensity changes occur if a mass arranged with a 38.7-nm axial periodicity moves in the direction of the unit cells, as indicated in Fig. 4. This mass can be either the troponin complex or myosin attached to the target zone on actin, in which actin monomers are favorably oriented for interaction with myosin. As shown in Fig. 4B, the troponin structural change and/or movement that explains the reciprocal intensity change would be too great to be realistic. On the other hand, a ~30° azimuthal swing of the myosin head around actin would much more easily explain the reciprocal change.

The myosin swing may trigger SA in the following way: During the stretch phase, myosin heads are loosely attached to the actin target zone in a low-force form. The pull of these myosin heads results in a concerted mass movement in the unit cell and, at the same time, converts them to a strongly bound, force-producing form, which enhances the myosin-binding signal. This conversion could, in turn, facilitate cooperative bind-

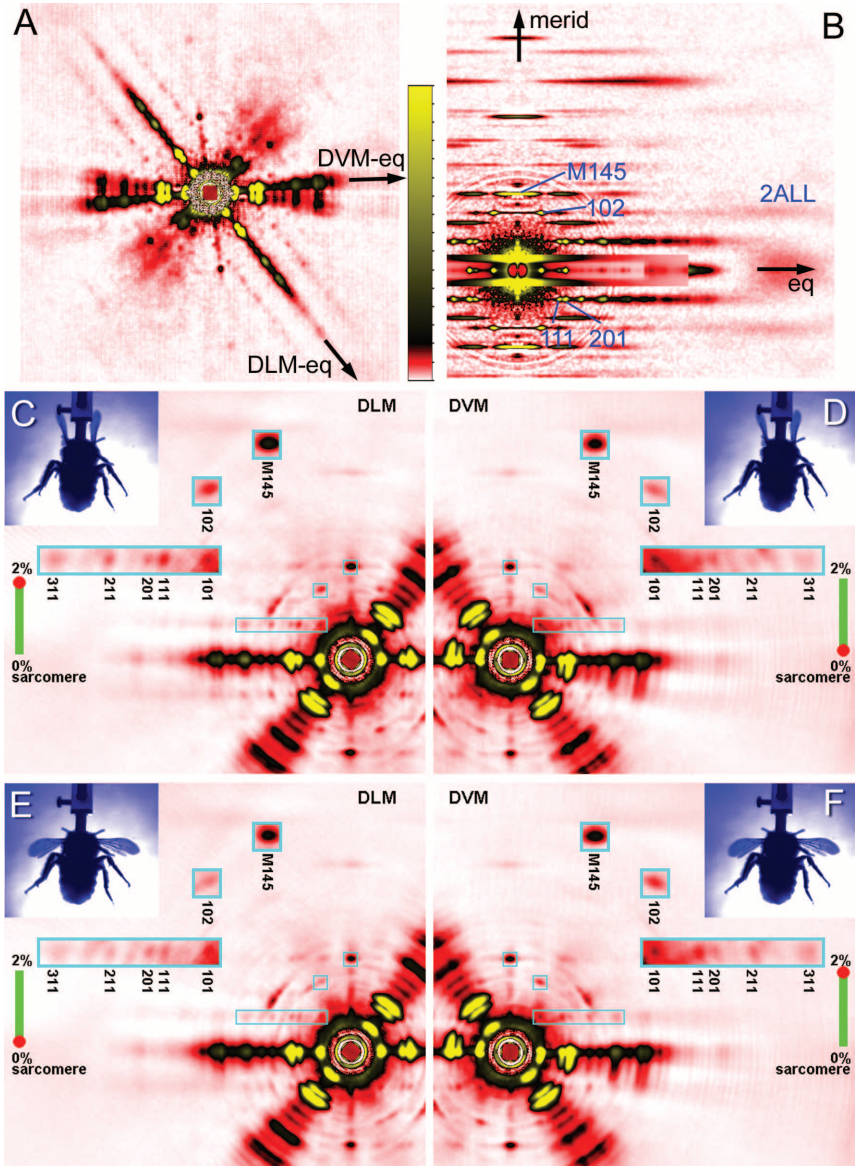


Fig. 2. Diffraction patterns recorded from flight muscles of live bumblebees, after background scattering subtraction (*12*, *25*). (**A**) A single frame of a movie recorded from a single bee (movie S2). The orientation of the pattern is as recorded. The axes of the muscle fibers are perpendicular to the equators (arrows). (**B**) A static diffraction pattern from skinned bumblebee IFM fibers for comparison. (**C** to **F**) Selected frames from movies (movies S4 and S5), in which data from all nine bees are summed after reorienting the patterns so that either of the equators for DLM or DVM is horizontal. (C and E) Equator of DLM horizontal. (D and F) Equator of DVM horizontal. The regions of interest (cyan boxes) are magnified in the same pictures.

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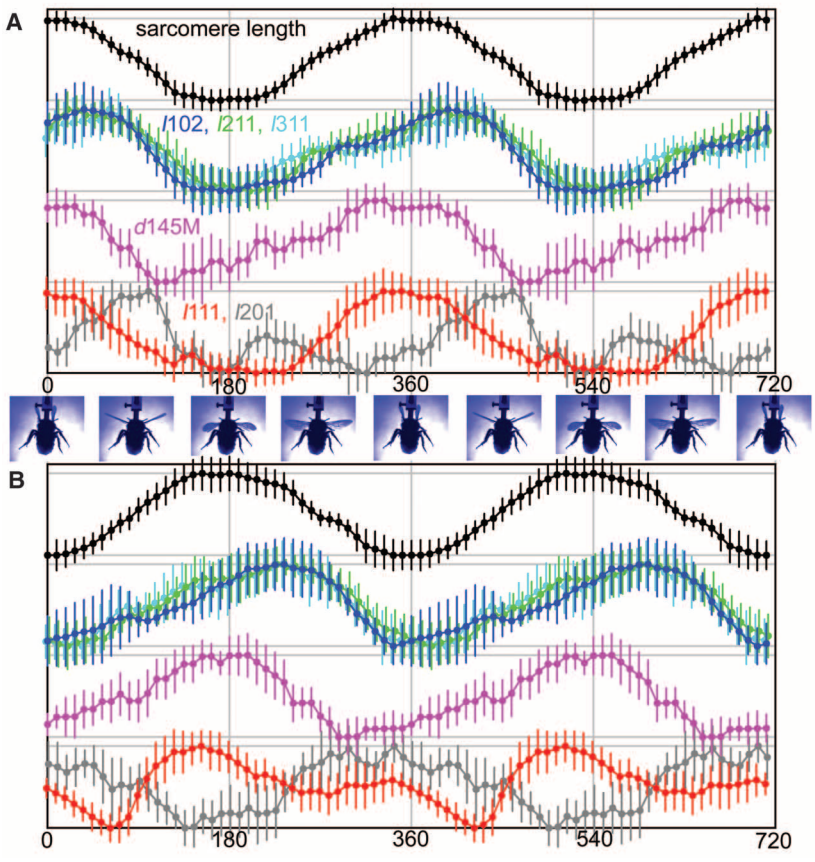


Fig. 3. Time courses of changes of various signals during wing-beat. (**A**) DLM; (**B**) DVM. The data, normalized to their maximum amplitude of change, are plotted against the phase of the wing beat. The phase is set to zero when the wings are upright. Plots are made for two wing-beat cycles. First row, the "length signal" (sarcomere length); second row, "myosin-binding singals" (intensities of 1,0,2; 2,1,1; and 3,1,1 reflections spots); third row, "force signal" (extension of myosin filaments); fourth row, "trigger signal" (intensities of 1,1,1 and 2,0,1 reflection spots). Signals were obtained by analyzing the summed patterns from nine bees, but the error bars (S.D.) were obtained by analyzing data from individual bees.

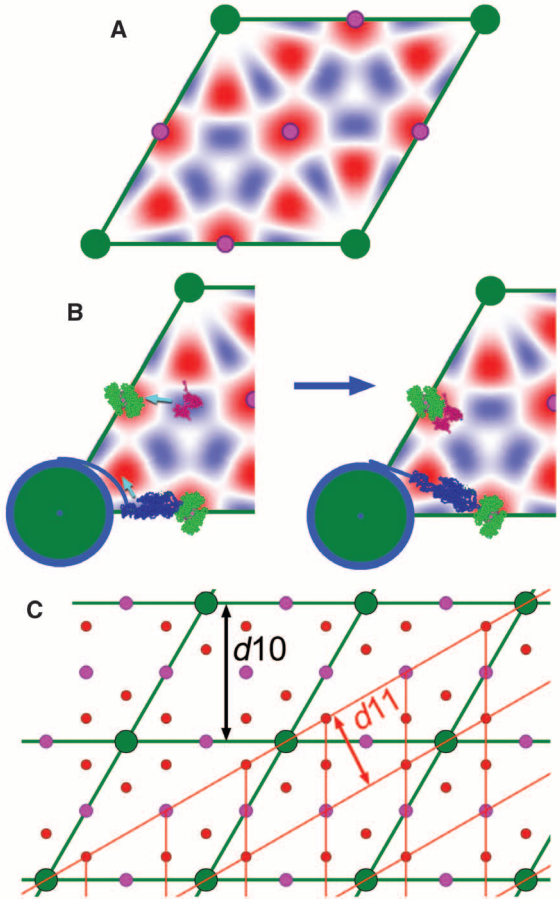


Fig. 4. Mass movement in the unit cell of filament lattice that accounts for the reciprocal intensity changes of the 1,1,1 and 2,0,1 reflection spots. (**A**) The regions in which the 1,1,1 spot is stronger than 2,0,1 (red) and vice versa (blue) when a mass is located there. Green and magenta circles represent thick and thin filaments, respectively. The reciprocal intensity changes will occur when the mass travels between the regions of different colors. As the mass must follow the symmetry of the $P6_4$ space group, it must be either troponin or myosin associated with the actin target zone. (**B**) Troponin (purple) and myosin head (dark blue) movements that would reproduce the reciprocal intensity changes. Thick filaments are drawn in their actual size. (**C**) New sublattices formed by myosin movement toward the red point. Their unit cell size is equal to the $d1,1$ spacing of the original unit cell. This explains the enhancement of the 1,1,1 spot.

ing of other myosin heads. This view is consistent with recent observations made by cryoelectron tomography (*7*, *8*), which show a substantial number of weakly binding myosin cross-bridges in contracting *Lethocerus* IFM. These studies also show that the myosin power stroke involves an azimuthal swing around actin that generates torque. If so, a stretch of IFM could apply reverse torque to weakly binding bridges, causing a ~30° rotation around actin. If correct, the basic mechanism for SA may be built into myosin itself, with myosin and actin being the minimum requirements, although evidence shows that troponin and tropomyosin are certainly implicated in SA (*10*, *12*, *21*). The near-crystalline sarcomeric structure of IFM may be best suited for such rotation to occur systematically.

The stretch-induced conversion from low-force to force-producing forms was initially proposed for vertebrate skeletal muscle to explain its response to stretch (*22*). A similar mechanism has been proposed for skinned IFM preparations (*9*, *23*). Such a mechanism could also explain the large force production in eccentric contractions and muscles stretched at the onset of a twitch [the classical active-state experiment (*24*)]. Insects may have evolved a way to maximize the efficiency of contractile mechanisms that already existed in their ancestral form, which vertebrate skeletal muscle also shares. If so, more detailed studies of IFM will further deepen our understanding of the functions of our own muscles.

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Supplementary Materials

www.sciencemag.org/cgi/content/full/science.1237266/DC1
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Figs. S1 to S3
Table S1
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Noncanonical Inflammasome Activation by Intracellular LPS Independent of TLR4

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Gram-negative bacteria including *Escherichia coli*, *Citrobacter rodentium*, *Salmonella typhimurium*, and *Shigella flexneri* are sensed in an ill-defined manner by an intracellular inflammasome complex that activates caspase-11. We show that macrophages loaded with synthetic lipid A, *E. coli* lipopolysaccharide (LPS), or *S. typhimurium* LPS activate caspase-11 independently of the LPS receptor Toll-like receptor 4 (TLR4). Consistent with lipid A triggering the noncanonical inflammasome, LPS containing a divergent lipid A structure antagonized caspase-11 activation in response to *E. coli* LPS or Gram-negative bacteria. Moreover, LPS-mutant *E. coli* failed to activate caspase-11. *Tlr4*$^{-/-}$ mice primed with TLR3 agonist polyinosinic:polycytidylic acid [poly(I:C)] to induce pro-caspase-11 expression were as susceptible as wild-type mice were to sepsis induced by *E. coli* LPS. These data unveil a TLR4-independent mechanism for innate immune recognition of LPS.

Canonical inflammasome proteins NLRP3 and NLRC4 engage the adaptor protein ASC and activate caspase-1 to promote cleavage and secretion of interleukin-1β (IL-1β) and IL-18, as well as cell death termed "pyroptosis" (*1*–*4*). Gram-negative bacteria such as *Escherichia coli* elicit noncanonical activation of caspase-1 in that caspase-11 (*5*, *6*) is required in addition to NLRP3 and ASC. Intriguingly, caspase-11 but neither NLRP3, ASC, nor caspase-1 is required for pyroptosis in response to Gram-negative bacteria (fig. S1A) (*7*). In mice, caspase-11 is critical to the immune response to Gram-negative bacteria (*7*–*12*), but the bacterial pathogen-associated molecular pattern (PAMP) that is responsible for triggering the noncanonical inflammasome is unknown.

Mouse bone marrow–derived macrophages (BMDMs) activate the noncanonical inflammasome in response to a combination of *E. coli* lipopolysaccharide (LPS) and cholera toxin B (CTB) (*7*). CTB is the nonenzymatic carbohydrate-binding component of the holotoxin (*13*). Inflammasome activity, be it canonical or noncanonical, appears to require two signals. A priming signal increases expression of inflammasome components, including pro-IL-1β, pro-caspase-11, and NLRP3, and then another signal triggers caspase activation (fig. S1, A to C) (*3*, *7*, *14*, *15*). We observed that LPS from only one *E. coli* serotype, O111:B4, combined with CTB to elicit caspase-1 processing, the secretion of IL-1β and IL-18, and pyroptosis (Fig. 1A and fig. S2, A and B). This finding was unexpected because triggering of the canonical NLRP3 inflammasome by adenosine 5′-triphosphate (ATP) was not dependent on the LPS serotype.

LPS from *E. coli* is composed of a conserved, Toll-like receptor 4 (TLR4)–activating moiety called lipid A, a core oligosaccharide, and a hyperdivergent O-specific polysaccharide (OPS) chain (fig. S2C) (*16*). Lipid A failed to produce noncanonical inflammasome activity when combined with CTB (Fig. 1A and fig. S2, A and B). We considered that LPS O111:B4 might be unique in up-regulating expression of pro-caspase-11, but lipid A and the different LPS O-serotypes induced comparable expression of pro-caspase-11 (fig. S2D). These data point to pro-caspase-11 induction being a consequence of lipid A engagement of TLR4 (*16*). Pam3CSK4 (TLR2 agonist) or R837 (TLR7 agonist) (*17*) that stimulate signaling via the adaptor protein MyD88 also induced expression of pro-caspase-11 (Fig. 1B and fig. S2E) (*7*), yet neither combined with CTB to promote pyroptosis or IL-1β secretion (fig. S2F). Even when BMDMs were primed with Pam3CSK4 in advance, only LPS O111:B4/CTB caused caspase-11–dependent secretion of IL-1β (Fig. 1C) and pyroptosis (fig. S2G). Therefore, a distinct property of LPS O111:B4, beyond priming, enables it and CTB to trigger the noncanonical inflammasome.

CTB binds to the pentasaccharide moiety of the GM1 gangliosaccharide (*13*, *18*). We found that LPS O111:B4, or its OPS chain alone (*19*), could bind to CTB, whereas LPS O55:B5 or lipid A could not (Fig. 1D and fig. S3A). Given that binding of CTB to GM1 on the cell surface promotes endocytosis of the cholera toxin complex (*13*, *18*), we investigated whether CTB delivers LPS O111:B4 into the cell. Consistent

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with this hypothesis, CTB increased BMDM uptake of LPS O111:B4, but not LPS O55:B5 (Fig. 1E and fig. S3, B to D). In addition, soluble GM1 attenuated uptake of CTB (fig. S3C) and CTB/LPS O111:B4 (Fig. 1F), and this coincided with reduced IL-1β secretion in response to CTB/LPS.

Next, we explored whether CTB was dispensable for noncanonical inflammasome activation if LPS was transfected into BMDMs (fig. S4, A and B). LPS transfection stimulated caspase-11–dependent pyroptosis and caspase-11, caspase-1, NLRP3, and ASC-dependent secretion of IL-1β and IL-18, irrespective of LPS serotype or whether the cells were primed with Pam3CSK4 (Fig. 1G and fig. S4, C to F). BMDMs electroporated with LPS gave similar results (fig. S4, G and H). We conclude that *E. coli* LPS of any serotype can trigger the noncanonical inflammasome if it gets into the cell. Hereafter, we used LPS O111:B4 unless specified.

Because the hexa-acylated lipid A moiety within *E. coli* LPS stimulates signaling by TLR4 (fig. S5A) (*16*), we tested whether intracellular lipid A triggers the noncanonical inflammasome. BMDMs were primed with Pam3CSK4 so as to circumvent the different priming efficiencies of lipid A and LPS. Transfection (Fig. 2, A and B, and fig. S5B) or electroporation (fig. S5C) of synthetic monophosphoryl lipid A stimulated caspase-11–dependent secretion of IL-1β and IL-18, pyroptosis, and the release of cleaved caspase-1. In contrast, the tetra-acylated lipid IVa precursor of lipid A had mouse TLR4 agonist activity (fig. S5A) (*20*, *21*) but was a poor trigger of the noncanonical inflammasome. Therefore, intracellular lipid A triggers the noncanonical inflammasome, but its sensor probably recognizes a different part of the molecule than TLR4.

Lipid A is conserved among different serotypes of *E. coli*, but several pathogenic Gram-negative bacteria make a modified lipid A and evade TLR4-mediated immune surveillance. For example, *Heliobacter pylori* makes a tetra-acyl lipid A moiety with long carbon fatty acid chains that stimulates TLR4 poorly (*20*, *22*, *23*). LPS from *H. pylori* or *Rhizobium galegae* (*24*) elicited little TLR4 signaling in BMDMs (fig. S5A). Their divergent lipid A moieties also failed to trigger the noncanonical inflammasome after transfection (Fig. 2, B and C, and fig. S5, D and E). In contrast, LPS from *Salmonella typhimurium*, which has a similar lipid A structure to that of *E. coli*, stimulated robust TLR4 signaling (fig. S5A) (*16*) and noncanonical inflammasome activity (Fig. 2C and fig. S5, D and E). These data suggest that lipid A modifications in pathogenic bacteria combat caspase-11–mediated surveillance mechanisms.

TLR4 plays a central role in detecting LPS (*25*, *26*), but our experiments with lipid IVa implied that TLR4 does not trigger the noncanonical inflammasome. We sought genetic proof with *Tlr4*$^{-/-}$ BMDMs that were primed with either Pam3CSK4 or poly(I:C). These cells responded just like wild-type BMDMs to intracellular LPS or lipid A in that they released cleaved caspase-1, IL-1β, IL-18, and lactate dehydrogenase (LDH) (Fig. 3, A and B, and fig. S6, A to D). MD-2 and MD-1 are the lipid A-binding proteins that complex with TLR4 and its homolog RP105, respectively (*27*). BMDMs lacking these proteins also exhibited normal noncanonical inflammasome activity, as did BMDMs lacking RP105 or the LPS coreceptor CD14 (fig. S6E). Therefore, TLR4, RP105, CD14, MD-1, and MD-2 are all dispensable for intracellular LPS to trigger the noncanonical inflammasome. The existence of multiple sensors that recognize the same PAMP is not without precedence: Both TLR5 and NLRC4 sense bacterial flagellin (*28*–*30*).

TLR4 signaling via the adaptor protein TRIF produces type I interferons (IFN-α and IFN-β) that induce pro-caspase-11 expression (*8*, *9*, *12*). Whether these IFNs play a role beyond priming BMDMs is unknown. We primed BMDMs lacking either the type I IFN receptor or TRIF with Pam3CSK4, which signals via MyD88 rather than TRIF (fig. S2E) (*17*). Subsequent transfection or

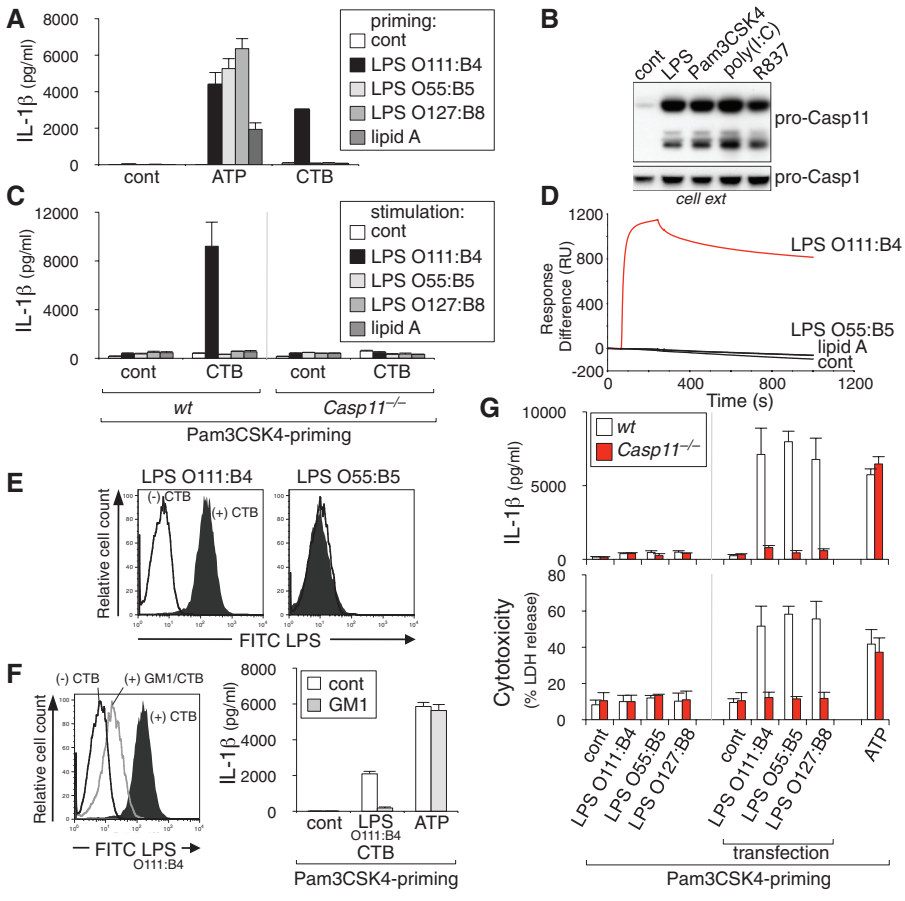


Fig. 1. Triggering of the noncanonical inflammasome by cytoplasmic LPS. (**A**) IL-1β released from BMDMs that were cultured for 6 hours in medium (cont), the indicated LPS serotypes, or lipid A and then supplemented with additional medium (cont) or CTB for 16 hours, or ATP for 4 hours. (**B**) Western blots to detect pro-caspase-11 in BMDMs cultured for 6 hours with the PAMPs indicated. (**C**) IL-1β secreted from wt or *Casp11*$^{-/-}$ BMDMs that were primed with Pam3CSK4 and then stimulated for 16 hours with the indicated LPS serotypes or lipid A in medium alone (cont) or in combination with CTB. (**D**) Binding of LPS O111:B4 to CTB by surface plasmon resonance. (**E** and **F**) Flow cytometry histograms showing labeling of BMDMs with fluorescein isothiocyanate (FITC)–conjugated LPS O111:B4 and LPS O55:B5 in the presence or absence of soluble GM1. Bar graph indicates the effect of soluble GM1 on IL-1β secretion from BMDMs stimulated for 16 hours with LPS plus CTB or 4 hours with ATP. (-) CTB indicates FITC-LPS alone. (**G**) IL-1β and LDH (used to measure cytotoxicity) released from primed BMDMs after culture or transfection with LPS for 16 hours. Graphs show the mean ± SD of triplicate wells and are representative of three independent experiments.

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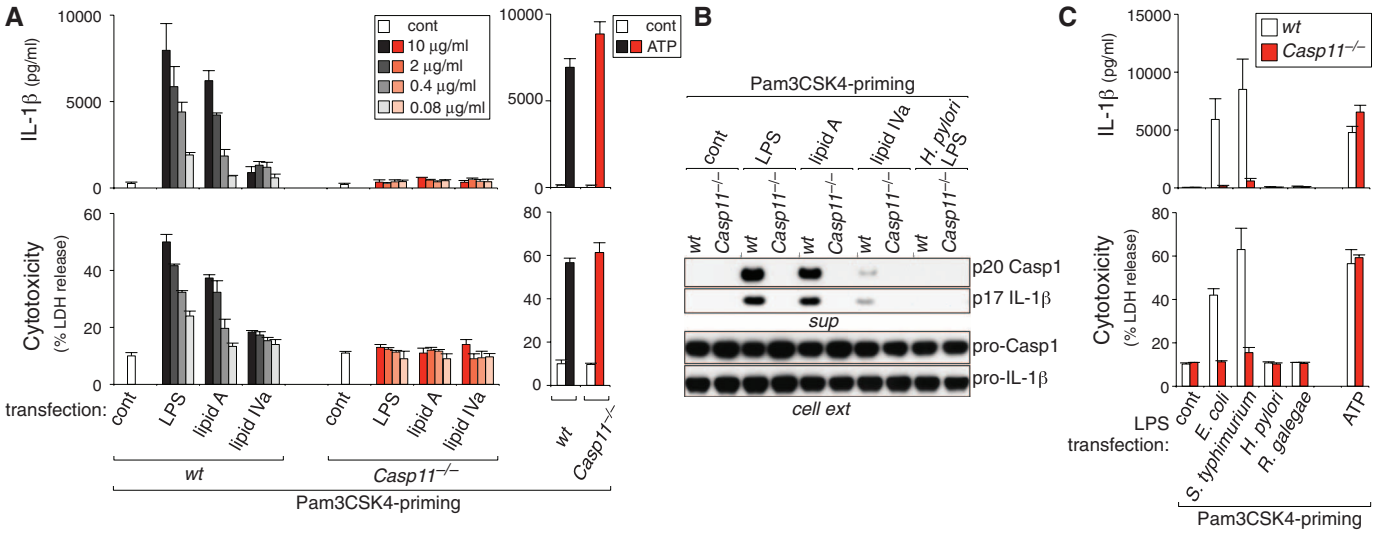


Fig. 2. Lipid A triggers the noncanonical inflammasome. (**A**) IL-1β and LDH released from wt and *Casp11*$^{-/-}$ BMDMs at 16 hours after transfection with LPS, synthetic monophosphoryl lipid A, or lipid IVa. (**B**) Western blots to detect pro-caspase 1, pro-IL-1β, cleaved IL-1β (p17), and cleaved caspase-1 (p20) from BMDMs transfected with *E. coli* LPS or lipid A for 16 hours. (**C**) IL-1β and LDH released by BMDMs at 16 hours after transfection with LPS from different bacteria. Graphs show the mean ± SD of triplicate wells and are representative of three independent experiments.

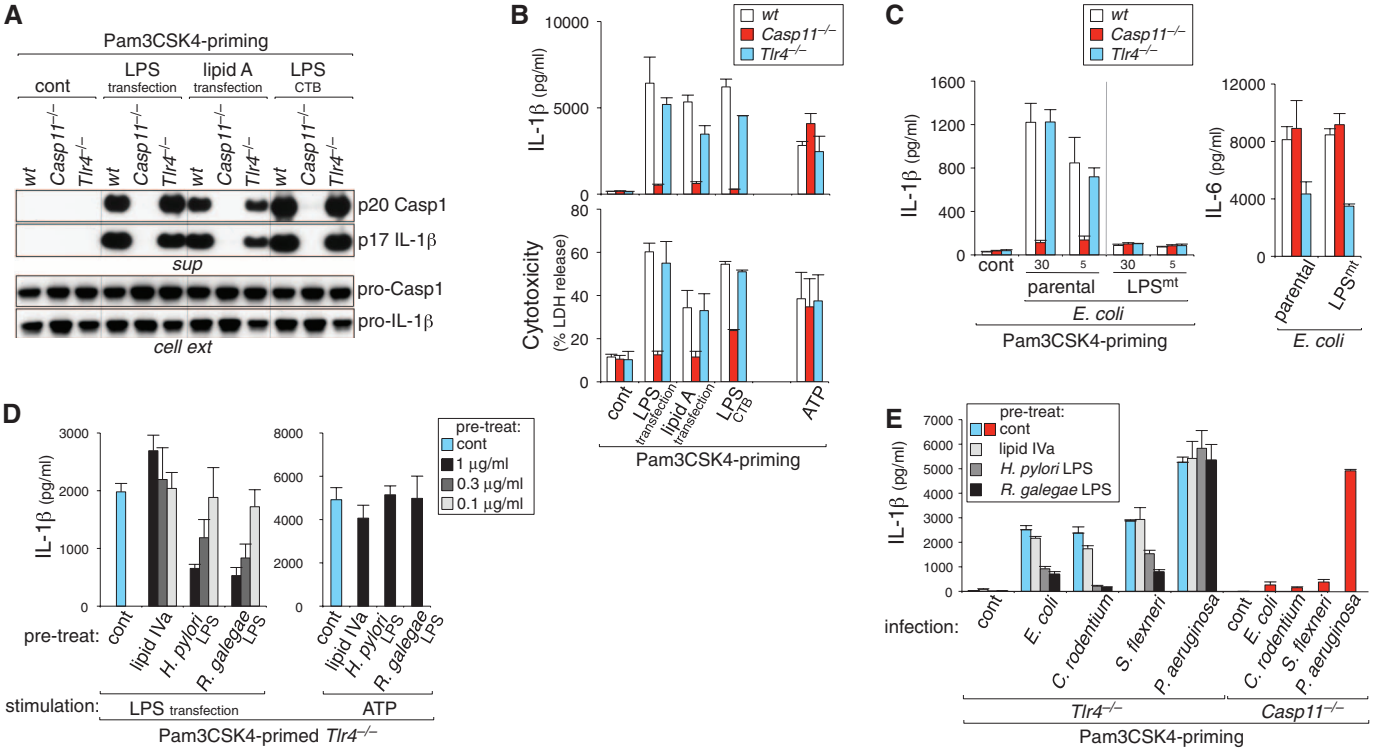


Fig. 3. TLR4 is dispensable for triggering of the noncanonical inflammasome by cytoplasmic LPS. (**A**) Western blots showing IL-1β and caspase-1 that is released from BMDMs at 16 hours after *E. coli* LPS or lipid A is delivered by transfection or CTB. Control cells were transfected with medium alone (cont). (**B**) IL-1β and LDH released by wt, *Tlr4*$^{-/-}$, and *Casp11*$^{-/-}$ BMDMs at 16 hours after delivery of *E. coli* LPS or lipid A. (**C**) IL-1β and IL-6 secreted from BMDMs infected with *E. coli* W3110 (parental) or CMR300 (LPS^{mt} lacking mature LPS) for 16 hours. The multiplicity of infection is indicated on the *x* axis or was 5. (**D**) IL-1β secreted by *Tlr4*$^{-/-}$ BMDMs transfected for 2 hours with dimethyl sulfoxide (cont), lipid IVa, or LPS (from *H. pylori* or *R. galegae*) and then transfected with LPS from *E. coli* for 16 hours or cultured with ATP for 4 hours. (**E**) IL-1β secreted by BMDMs transfected for 2 hours as in (D) and then infected with the bacteria indicated for 16 hours. Graphs show the mean ± SD of triplicate wells and are representative of three independent experiments.

electroporation with LPS caused *Ifnar*$^{-/-}$ and *Trif*$^{-/-}$ BMDMs to secrete IL-1β and undergo pyroptosis to the same extent as wild type or *Tlr4*$^{-/-}$ BMDMs (fig. S6F). Therefore, the entire TLR4-TRIF–type I IFN pathway is dispensable for intracellular LPS to trigger the noncanonical inflammasome. Previously, induction of pro-caspase-11 protein and its autoproteolysis was proposed to be sufficient to engage the noncanonical inflammasome (*9*). We

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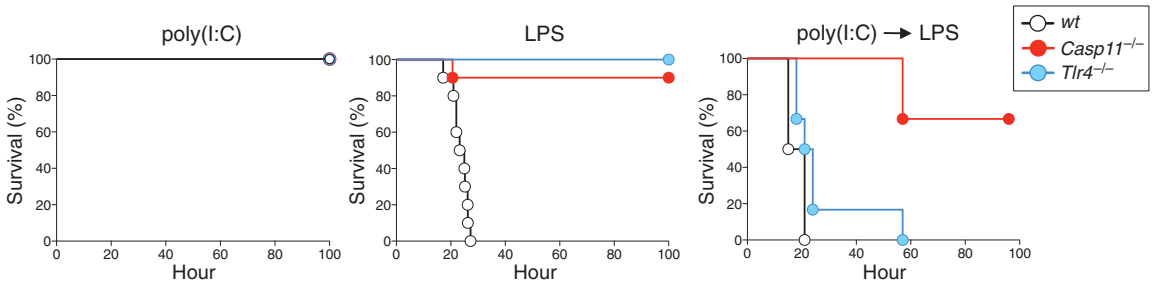


Fig. 4. Lethal sepsis mediated by TLR4-independent sensing of LPS. Kaplan-Meier survival plots for mice challenged with 4 mg/kg poly(I:C), 54 mg/kg LPS, or poly(I:C) followed by LPS. Experiments used 6 to 10 mice of each genotype. Data are representative of four independent experiments. Adjusted *P* values are supplied in table S1.

believe that this scenario is unlikely because LPS transfection triggered pyroptosis in primed *Tlr4*$^{-/-}$ BMDMs despite unchanging pro-caspase-11 levels (fig. S6G).

To address the role of LPS in triggering the noncanonical inflammasome during a Gram-negative bacterial infection, we primed wild type and *Tlr4*$^{-/-}$ BMDMs with Pam3CSK4 and then infected them with either *E. coli* "wild-type" strain W3110 (parental) or the LPS-mutant derivative strain CMR300 (LPSmt), the latter lacking mature hexa-acyl lipid A and accumulating the tetra-acyl lipid IVa precursor because of a defect in LPS biosynthesis (*31*). W3110 bacteria triggered caspase-11–dependent IL-1β secretion (Fig. 3C) and pyroptosis (fig. S6H) in both wild type and *Tlr4*$^{-/-}$ BMDMs, whereas the LPS-mutant CMR300 strain did not. The two strains of *E. coli* did, however, stimulate comparable IL-6 production, which is consistent with lipid IVa being a mouse TLR4 agonist (fig. S5A) (*20*, *21*). In addition, *Tlr4*$^{-/-}$ BMDMs preloaded with LPS from *H. pylori* or *R. galegae* exhibited less caspase-11–dependent secretion of IL-1β when they were subsequently transfected with LPS from *E. coli* (Fig. 3D) or infected with Gram-negative bacteria (Fig. 3E). This antagonistic effect of LPS from *H. pylori* or *R. galegae* was specific to the noncanonical inflammasome because IL-1β secretion in response to canonical stimuli ATP or *Pseudomonas aeruginosa* (*3*, *7*, *32*) was not impaired. Collectively, these data indicate that macrophages use the noncanonical inflammasome to sense intracellular LPS during a Gram-negative bacterial infection, and they explain why noncanonical inflammasome activity is not observed with Gram-positive bacteria (*7*–*12*). Although it is unclear exactly where in the cell the noncanonical inflammasome is activated during bacterial infection, a cytosolic location has been proposed (*10*, *11*).

We investigated the relevance of our in vitro findings with a mouse model of acute septic shock. Wild type, *Casp11*$^{-/-}$, and *Tlr4*$^{-/-}$ mice were challenged with a lethal dose of LPS, and consistent with previous reports (*7*, *25*, *26*, *33*), caspase-11 or TLR4 deficiency conferred resistance, with 9 out of 10 *Casp11*$^{-/-}$ mice and 10 out of 10 *Tlr4*$^{-/-}$ mice surviving (Fig. 4). The caveat of this study is that LPS-challenged *Tlr4*$^{-/-}$ mice probably fail to induce pro-caspase-11. We circumvented this priming issue by pretreating the mice with a nonlethal dose of the TLR3 agonist poly(I:C) (Fig. 4 and fig. S7A). Subsequent LPS challenge caused morbidity in all *Tlr4*$^{-/-}$ and wild-type mice within 60 hours, whereas the onset of morbidity in the *Casp11*$^{-/-}$ mice was delayed significantly (Fig. 4 and table S1). Therefore, both TLR4-dependent and -independent mechanisms for sensing LPS contribute to this model of lethal sepsis (fig. S7B). Lethal sepsis is probably driven by caspase-11–dependent pyroptosis rather than caspase-1–dependent secretion of IL-1β and IL-18 because *Casp1*$^{-/-}$ mice are as susceptible to LPS as wild-type mice are (*7*). We postulate that high-dose LPS is sufficient to trigger the noncanonical inflammasome in vivo because BMDMs cultured with large quantities of LPS display spontaneous LPS internalization (fig. S7C) (*34*, *35*). It is unclear, however, which cell types trigger the noncanonical inflammasome to drive lethal sepsis in vivo.

We show that the hexa-acyl lipid A moiety of LPS from *E. coli* or *S. typhimurium* is sensed inside the macrophage, albeit in an ill-defined manner, and this triggers caspase-11 activation by the noncanonical inflammasome. The resistance of mice lacking caspase-11 to LPS-induced lethality suggests that antagonists of the activation of human caspases 4 and 5 (the orthologs of mouse caspase-11) may benefit patients suffering from sepsis.

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Supplementary Materials

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Cytoplasmic LPS Activates Caspase-11: Implications in TLR4-Independent Endotoxic Shock

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Inflammatory caspases, such as caspase-1 and -11, mediate innate immune detection of pathogens. Caspase-11 induces pyroptosis, a form of programmed cell death, and specifically defends against bacterial pathogens that invade the cytosol. During endotoxemia, however, excessive caspase-11 activation causes shock. We report that contamination of the cytoplasm by lipopolysaccharide (LPS) is the signal that triggers caspase-11 activation in mice. Specifically, caspase-11 responds to penta- and hexa-acylated lipid A, whereas tetra-acylated lipid A is not detected, providing a mechanism of evasion for cytosol-invasive *Francisella*. Priming the caspase-11 pathway in vivo resulted in extreme sensitivity to subsequent LPS challenge in both wild-type and *Tlr4*-deficient mice, whereas *Casp11*-deficient mice were relatively resistant. Together, our data reveal a new pathway for detecting cytoplasmic LPS.

Caspases are evolutionarily ancient proteases that are integral to basic cellular physiology. Although some caspases mediate apoptosis, the inflammatory caspases-1 and -11 trigger pyroptosis, a distinct form of lytic programmed cell death. In addition, caspase-1 processes interleukin-1β (IL-1β) and IL-18 to their mature secreted forms. Caspase-1 is activated by the canonical inflammasomes, which signal via the adaptor ASC; NLRC4 and NLRP1a and -1b can additionally activate caspase-1 directly (*1*, *2*). In contrast to caspase-1, caspase-11 is activated independently of all known canonical inflammasome pathways; the hypothetical caspase-11–activating platform has been termed the noncanonical inflammasome (*3*). *Casp1*$^{-/-}$ mice generated from 129 background stem cells are also deficient in *Casp11* because of a passenger mutation backcrossed from the 129 background into C57BL/6. Caspase-11 is responsible for certain phenotypes initially attributed to caspase-1, such as shock after endotoxin challenge (*3*). The physiologic function of caspase-11 is to discriminate cytosolic from vacuolar bacteria (*4*). In the absence of caspase-11, mice become acutely susceptible to infection by bacteria that escape the phagosome and replicate in the cytosol, such as *Burkholderia pseudomallei* and *B. thailandensis* (*4*). Caspase-11 also responds to vacuolar Gram-negative bacteria, albeit with delayed kinetics (*3*, *5*–*7*), which may have relevance to its aberrant activation during sepsis. Although these studies demonstrated both detrimental and protective roles for caspase-11, the precise nature of the caspase-11–activating signal remained unknown.

Because caspase-11 specifically responds to cytosolic bacteria, we hypothesized that detection of a conserved microbial ligand within the cytosol triggers caspase-11. To address this hypothesis, we generated lysates of Gram-negative and Gram-positive bacteria and transfected them into lipopolysaccharide (LPS)–primed *Nlrc4*$^{-/-}$*Asc*$^{-/-}$*Casp11*$^{+/+}$ or *Casp1*$^{-/-}$*Casp11*$^{-/-}$ bone marrow–derived macrophages (BMMs). By comparing these strains, we can examine caspase-11 activation in the absence of canonical inflammasome detection of flagellin and DNA (fig. S1). Although boiled Gram-negative bacterial lysates were detected through caspase-11 upon transfection into BMMs, Gram-positive lysates were not (Fig. 1A). Ribonuclease (RNase), deoxyribonuclease (DNase), lysozyme, and proteinase K digestion was sufficient to dispose of canonical inflammasome agonists but failed to eliminate the caspase-11–activating factor (or factors) (Fig. 1B). We then treated boiled lysates with ammonium hydroxide, which is known to deacylate lipid species (*8*), and observed that the caspase-11–activating factor was degraded, whereas canonical inflammasome agonists persisted (Fig. 1C).

These results suggested LPS as the caspase-11 agonist. Consistent with this hypothesis, BMMs underwent caspase-11–dependent pyroptosis after transfection of ultrapure *Salmonella minnesota* RE595 LPS (Fig. 1D). Caspase-11 can promote IL-1β secretion by triggering the canonical NLRP3 pathway (fig. S1) (*3*). Consistently, IL-1β secretion and caspase-1 processing after transfection of LPS were also caspase-11 dependent (Fig. 1, E to G). Moreover, caspase-11 alone promoted pyroptosis (Fig. 1H). In contrast to caspase-1, we were unable to convincingly visualize caspase-11 processing by means of Western blot (Fig. 1, F and G, and fig. S2A), despite the vast majority of cells exhibiting pyroptotic morphology as seen by phase microscopy. Although these data do not exclude the possibility that processing of a small amount of caspase-11 is required for pyroptosis, they do indicate that processing is not a good proxy measure for rapid caspase-11 activation. This is consistent with direct caspase-1 activation by NLRC4, which is not accompanied by processing (*9*). These results suggest that the presence of LPS in the cytosol is sufficient to trigger caspase-11; however, we cannot rule out the formal possibility that this signaling arises from a membrane-bound compartment such as the endoplasmic reticulum or golgi. Future identification of the noncanonical inflammasome will permit this determination.

The caspase-11 pathway is not responsive unless macrophages are previously stimulated (primed) with either LPS, polyinosinic:polycytidylic acid [poly(I:C)], interferon-β (IFN-β), or IFN-γ, which likely induces multiple components of the noncanonical inflammasome pathway, including caspase-11 (fig. S2B) (*4*–*7*, *10*). LPS and poly(I:C) prime via Toll-like receptor 4 (TLR4) and TLR3, respectively, which both stimulate IFN-β production; IFN-β and IFN-γ signaling overlap in their activation of the signal transducers and activators of transcription–1 (STAT1) transcription factor, which is critical to caspase-11 activation (*5*, *7*). In order to separate the priming and activation stimuli of caspase-11, we verified that poly(I:C) and IFN-γ could substitute for LPS as priming agents (Fig. 1I).

To corroborate our LPS transfection results, we sought another means to deliver LPS to the cytoplasm. *Listeria monocytogenes* lyses the phagosome via the pore-forming toxin listeriolysin O (LLO) and, as a Gram-positive bacterium, does not contain LPS. *L. monocytogenes* infection did not activate caspase-11 in BMMs; however, co-phagocytosis of wild-type, but not LLO mutant (Δ*hly*), *L. monocytogenes* with exogenous LPS triggered pyroptosis, IL-1β secretion, and caspase-1–processing dependent on caspase-11 (Fig. 2, A to F). Despite this genetic evidence of caspase-11 activation, we again did not observe proteolytic processing of caspase-11 (Fig. 2, E and F). In conjunction with our previous data indicating that caspase-11 discriminates cytosolic from vacuolar Gram-negative bacteria (*4*), these results indicate that detection of LPS in the cytoplasm triggers caspase-11–dependent pyroptosis.

Previous studies have shown that another agonist, cholera toxin B (CTB), activates caspase-11. However, LPS was present with CTB for the duration of these experiments (*3*), and caspase-11 failed to respond to CTB in the absence of LPS (Fig. 2G). The physiological function of CTB is to mediate the translocation of the enzymatically active cholera toxin A (CTA) into host cells. Therefore, we hypothesized that activation of caspase-11 by CTB results from delivery of co-phagocytosed LPS into the cytosol. Under this hypothesis, CTB should likewise be able to shuttle canonical inflammasome agonists, which are detected in the cytosol. Indeed, when LPS was replaced with PrgJ, an NLRC4 agonist (*11*), the pyroptotic response switched from caspase-11 dependence to NLRC4 dependence (Fig. 2G). Therefore, in these experiments CTB is not a caspase-11 agonist, but rather an LPS delivery agent. Whether CTB disrupts vacuoles during its use as an adjuvant or whether complete cholera toxin (CTA/CTB) disrupts vacuoles during infection with *Vibrio cholera* remain to be examined.

We next examined the LPS structural determinants required for detection through caspase-11 and found that the lipid A moiety alone was sufficient for activation (Fig. 3A). It is well established that lipid A modifications enable TLR4

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evasion, and we therefore hypothesized that cytosolic pathogens could evade caspase-11 by means of a similar strategy. Indeed, *Francisella novicida*, a Gram-negative cytosolic bacteria, was not detected by caspase-11 (no signal in *Nlrc4*$^{-/-}$*Asc*$^{-/-}$ BMMs) (Fig. 3B). *F. novicida* lysates containing DNA activated caspase-1; however, after DNase digestion the remaining LPS failed to activate caspase-11, which was not restored by temperature-dependent alterations in acyl chain length (Fig. 3C) (*12*). As with *L. monocytogenes*, co-phagocytosis of *F. novicida* with exogenous *S. minnesota* LPS resulted in caspase-11 activation (Fig. 3D). Together, these results suggest that *Francisella* species evade caspase-11 by modifying their lipid A. *Francisella* species have peculiar tetra-acylated lipid A unlike the hexa-acylated species of enteric bacteria (*13*). *F. novicida* initially synthesizes a penta-acylated lipid A structure with two phosphates and then removes the 4′ phosphate and 3′ acyl chain in reactions that do not occur in *lpxF* mutants (*14*, *15*) (Fig. 3E). Conversion to the penta-acylated structure restored caspase-11 activation, whereas other modifications that maintained the tetra-acylated structures [*flmK* mutant or 18°C growth (*12*, *16*)] did not (Fig. 3F). *lpxF* mutant lipid A is not detected by TLR4 (*14*), suggesting that the TLR4 and caspase-11 pathways have different structural requirements.

Deacylation of lipid A is a common strategy used by pathogenic bacteria. For example, *Yersinia pestis* removes two acyl chains from its lipid A upon transition from growth at 25°C to 37°C (Fig. 3G) (*17*). Consistent with our structural studies of *F. novicida* lipid A, caspase-11 detected hexa-acylated lipid A from *Y. pestis* grown at 25°C, but not tetra-acylated lipid A from bacteria grown at 37°C (Fig. 3H). Together, these data indicate that caspase-11 responds to distinct lipid A structures,

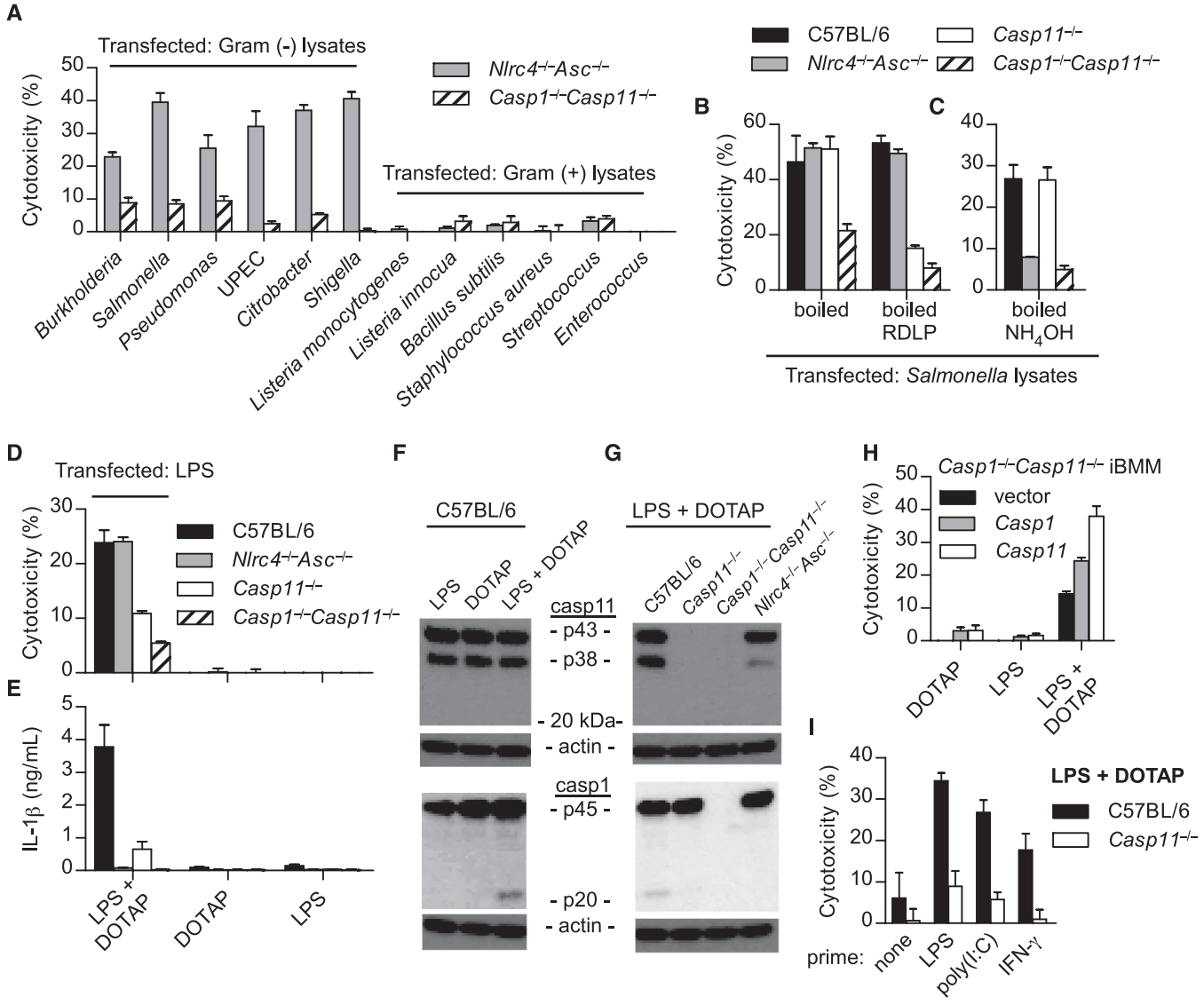


Fig. 1. Cytoplasmic LPS triggers caspase-11 activation. (**A** to **H**) BMM were LPS-primed overnight before transfection. [(A) to (C)] BMMs were transfected with the indicated bacterial lysates packaged in Lipofectamine 2000 (Invitrogen, Carlsbad, CA). Cytotoxicity was determined by lactate dehydrogenase release 4 hours later. Where indicated, lysates were treated with RNase, DNase, lysozyme, and proteinase K (RDLP) (B) or ammonium hydroxide (C). [(D and (E)] BMMs were transfected with ultrapure LPS from *S. minnesota* RE595 packaged with DOTAP (Roche, Mannheim, Germany), a liposomal transfection reagent. Cytotoxicity (D) and IL-1β secretion by means of enzyme-linked immunosorbent assay (E) were determined 4 hours after transfection. [(F) to (G)] BMMs were stimulated as in (D), and caspase-1 and -11 processing by means of Western blot were examined 2 hours after transfection. (H) Immortalized *Casp1*$^{-/-}$*Casp11*$^{-/-}$ BMMs (iBMMs) complemented by retroviral transduction of *Casp1* or *Casp11* were transfected with LPS from *S. minnesota* RE595. Cytotoxicity was determined after 4 hours. (**I**) Macrophages were primed overnight with LPS (50 ng/mL), poly(I:C) (1 μg/mL), IFN-γ (8 ng/mL), or left untreated. Cells were then transfected with LPS from *S. minnesota* RE595, and cytotoxicity was determined 2 hours later. Data are representative of at least three experiments. Error bars indicate SD of technical replicates.

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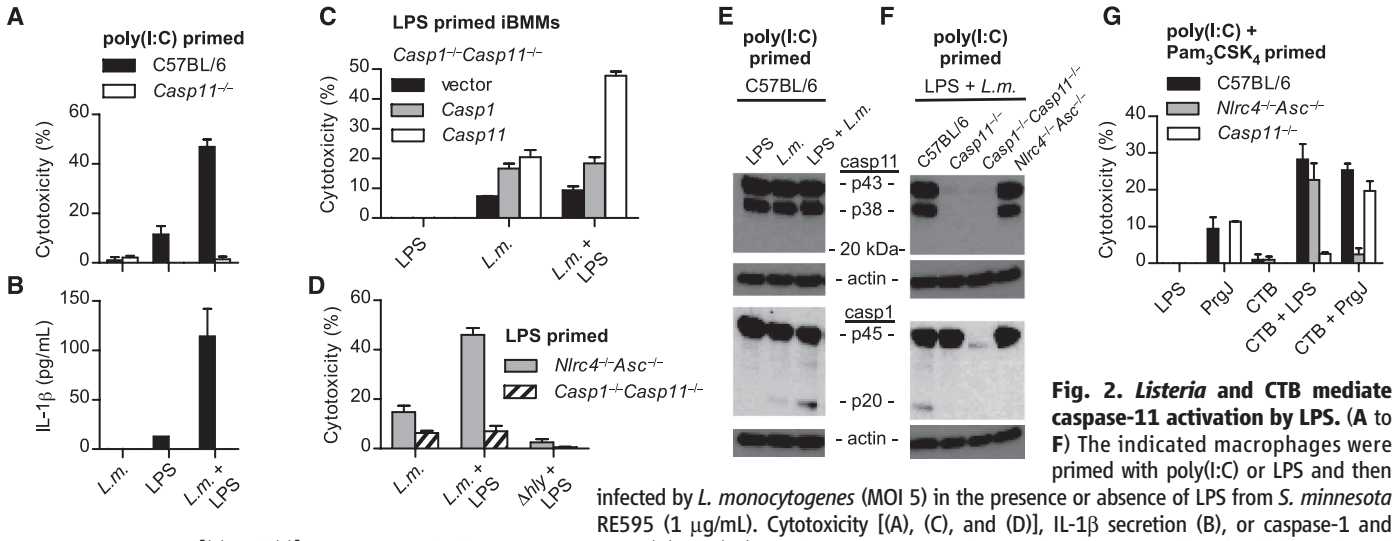


Fig. 2. *Listeria* and CTB mediate caspase-11 activation by LPS. (**A** to **F**) The indicated macrophages were primed with poly(I:C) or LPS and then infected by *L. monocytogenes* (MOI 5) in the presence or absence of LPS from *S. minnesota* RE595 (1 μg/mL). Cytotoxicity [(A), (C), and (D)], IL-1β secretion (B), or caspase-1 and caspase-11 processing [(E) and (F)] were examined 4 hours after infection. (**G**) Poly(I:C)– and Pam_3CSK_4–primed macrophages were incubated with the indicated combinations of CTB (20 μg/mL), LPS from *E. coli* O111:B4 (1 μg/mL), and Prg] (10 μg/mL). Cytotoxicity was determined 16 hours later. Data are representative of three [(A), (D), and (G)] or two [(B), (C), (E), and (F)] experiments. Error bars indicate SD of technical replicates.

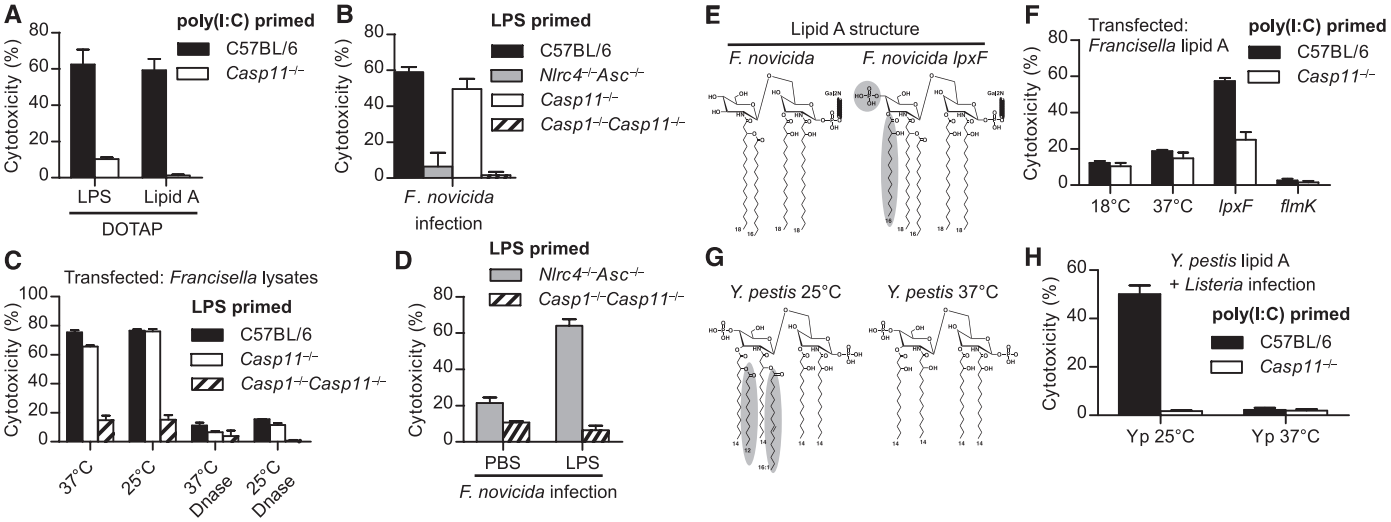


Fig. 3. Caspase-11 responds to distinct lipid A structures. (**A**) Poly(I:C)–primed BMMs were transfected with LPS from *S. minnesota* RE595 or *S. typhimurium* lipid A. Cytotoxicity was determined after 2 hours. (**B**) Cytotoxicity in LPS-primed BMMs was determined 4 hours after infection with *F. novicida* (MOI 200). (**C**) LPS-primed BMMs were transfected with mock or DNase-treated *F. novicida* lysates. Cytotoxicity was determined 4 hours later. (**D**) Macrophages were infected as in (B) in the presence or absence of LPS from *S. minnesota* RE595. (**E**) Structural comparison of lipid A from wild-type *F. novicida* or the *lpxF* mutant. Structural changes are indicated. (**F**) Poly(I:C)–primed macrophages were transfected with lipid A from *F. novicida* grown at 18°C or 37°C or the indicated *F. novicida* mutants grown at 37°C. Cytotoxicity was determined after 2 hours. (**G**) Structural comparison of lipid A from *Y. pestis* grown at 25°C or 37°C. (**H**) Poly(I:C)–primed BMMs were infected with *L. monocytogenes* in the presence of lipid A from *Y. pestis* grown at 25°C or 37°C. Cytotoxicity was determined after 4 hours. Data are representative of at least three [(A), (F), and (G)] or two [(B), (C), and (D)] experiments. Error bars indicate SD of technical replicates.

and pathogens appear to exploit these structural requirements in order to evade caspase-11.

In addition to detection of extracellular/vacuolar LPS by TLR4, our data indicate that an additional sensor of cytoplasmic LPS activates caspase-11. These two pathways intersect because TLR4 primes the caspase-11 pathway. However, *Tlr4*$^{-/-}$ BMMs responded to transfected or CTB-delivered LPS after poly(I:C) priming (Fig. 4, A to C). Therefore, caspase-11 can respond to cytoplasmic LPS independently of TLR4.

In established models of endotoxic shock, both *Tlr4*$^{-/-}$ and *Casp11*$^{-/-}$ mice are resistant to lethal challenge with 40 to 54 mg/kg LPS (*3*, *18*, *19*), whereas wild-type mice succumb in 18 to 48 hours (Fig. 4D). We hypothesized that TLR4 detects extracellular LPS and primes the caspase-11 pathway in vivo. Then, if high concentrations of LPS persist, aberrant localization of LPS within the cytoplasm could trigger caspase-11, resulting in the generation of shock mediators. We sought to separate these two events by priming and then challenging with otherwise sublethal doses of LPS. C57BL/6 mice primed with LPS rapidly succumbed to secondary LPS challenge in 2 hours (Fig. 4D). TLR4 was required for LPS priming because LPS-primed *Tlr4*$^{-/-}$ mice survived secondary LPS challenge (Fig. 4E). To determine whether alternate priming pathways could substitute for TLR4 in vivo, we primed mice with poly(I:C) and observed that both C57BL/6 and *Tlr4*$^{-/-}$ mice succumbed to secondary LPS challenge (Fig. 4E). This was concomitant with hypothermia (Fig. 4F), seizures, peritoneal fluid accumulation, and occasionally intestinal hemorrhage. In contrast, poly(I:C)–primed *Casp11*$^{-/-}$ mice were more resistant to secondary LPS challenge (Fig. 4G), demonstrating the consequences of aberrant caspase-11 activation. Collectively, our

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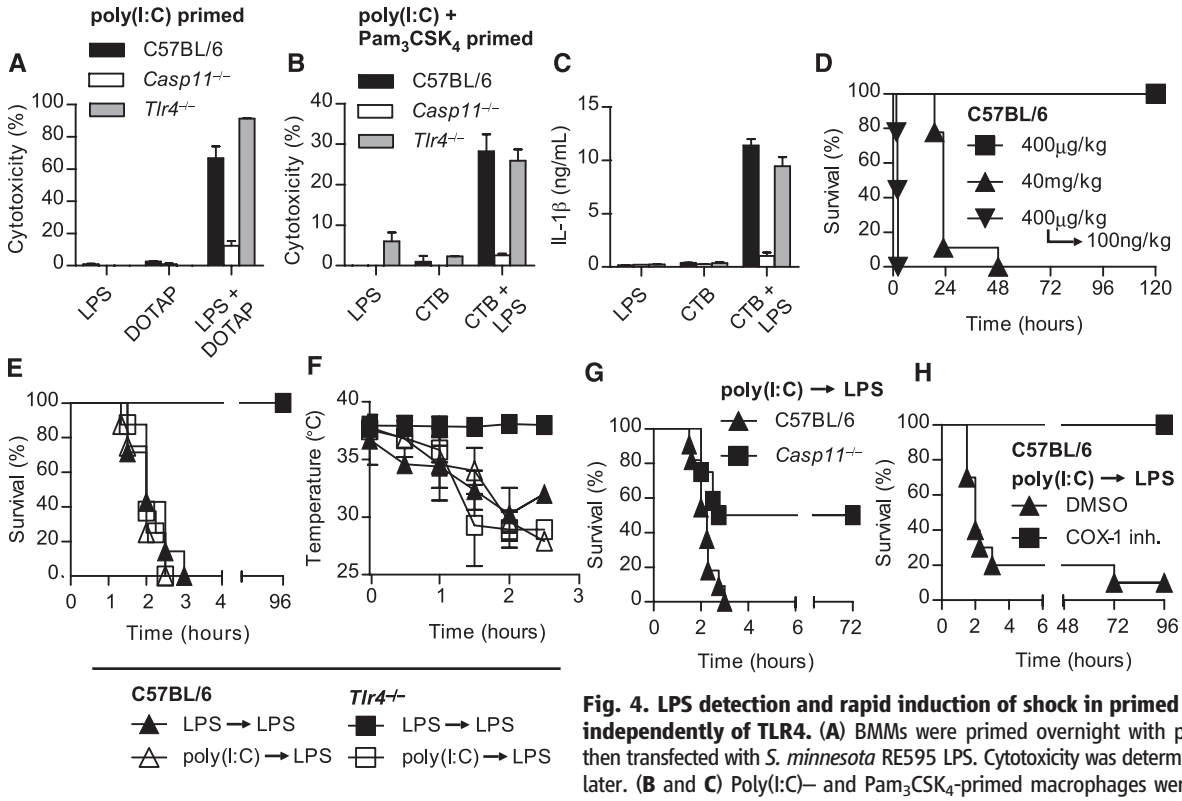


Fig. 4. LPS detection and rapid induction of shock in primed mice occur independently of TLR4. (**A**) BMMs were primed overnight with poly(I:C) and then transfected with *S. minnesota* RE595 LPS. Cytotoxicity was determined 2 hours later. (**B** and **C**) Poly(I:C)– and Pam_3CSK_4-primed macrophages were incubated with the indicated combinations of CTB (20 μg/mL) and LPS from *E. coli* O111:B4 (1 μg/mL). Cytotoxicity (B) and IL-1β secretion (C) were determined 16 hours later. Data are representative of at least three experiments; error bars indicate SD of technical replicates [(A) to (C)]. (**D**) Survival of mice challenged with the indicated doses of *Escherichia coli* LPS, or primed with LPS and then rechallenged 7 hours later. Data are pooled from three experiments; $n = 9$ mice per condition. (**E**) Survival of mice primed with LPS (400 μg/kg) or poly(I:C) (LMW, 10 mg/kg) and then challenged 7 hours later with LPS (100 ng/kg). Data are pooled from three experiments; $n = 7$ mice per LPS prime group and $n = 8$ mice for poly(I:C) prime group. (**F**) Rectal temperatures of mice in panel (E) after LPS challenge. Data are representative of three experiments; $n = 4$ mice per condition. (**G**) Survival of poly(I:C)–primed mice challenged 6 hours later with LPS (10 ng/kg). Data are pooled from three experiments, $n = 11$ mice (C57BL/6) or 12 (*Casp11*$^{-/-}$). (**H**) Mice were primed with poly(I:C) and then challenged 6 hours later with LPS (100 ng/kg) and monitored for survival. One hour before LPS challenge, mice were given 5 mg/kg of COX-1 inhibitor or dimethyl sulfoxide control. Data are pooled from two experiments; $n = 11$ mice per condition.

data indicate that activation of caspase-11 by LPS in vivo can result in rapid onset of endotoxic shock independent of TLR4.

Mice challenged with the canonical NLRC4 agonist flagellin coupled to the cytosolic translocation domain of anthrax lethal toxin also experience a rapid onset of shock (*20*). In this model, NLRC4-dependent caspase-1 activation triggers lethal eicosanoid production via COX-1 with similar kinetics to our prime-challenge model, suggesting convergent lethal pathways downstream of caspase-1 and caspase-11. Indeed, the COX-1 inhibitor SC-560 rescued poly(I:C)–primed mice from LPS lethality (Fig. 4H).

Although physiological activation of caspase-11 is beneficial in defense against cytosolic bacterial pathogens (*4*), its aberrant hyperactivation becomes detrimental during endotoxic shock. Our data suggest that when LPS reaches critical concentrations during sepsis, aberrant LPS localization occurs, activating cytosolic surveillance pathways. Clinical sepsis is a more complex pathophysiologic state, in which multiple cytokines, eicosanoids, and other inflammatory mediators are likely to be hyperactivated. Eicosanoid mediators and other consequences of pyroptotic cellular lysis (*21*) should be considered in future therapeutic options designed to treat Gram-negative septic shock. This underscores the concept that Gram-negative and Gram-positive sepsis may cause shock via divergent signaling pathways (*22*) and that treatment options should consider these as discreet clinical entities.

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Supplementary Materials

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Interacting Gears Synchronize Propulsive Leg Movements in a Jumping Insect

Malcolm Burrows† and Gregory Sutton*

Gears are found rarely in animals and have never been reported to intermesh and rotate functionally like mechanical gears. We now demonstrate functional gears in the ballistic jumping movements of the flightless planthopper insect *Issus.* The nymphs, but not adults, have a row of cuticular gear (cog) teeth around the curved medial surfaces of their two hindleg trochantera. The gear teeth on one trochanter engaged with and sequentially moved past those on the other trochanter during the preparatory cocking and the propulsive phases of jumping. Close registration between the gears ensured that both hindlegs moved at the same angular velocities to propel the body without yaw rotation. At the final molt to adulthood, this synchronization mechanism is jettisoned.

Many insects jump prodigiously by rapid and powerful movements of their hindlegs. Two arrangements of the hindlegs are found; those of grasshoppers and fleas move in separate planes at the side of the body; those of the champion jumping insects, froghoppers and planthoppers, move counterrotationally in approximately the same near-horizontal plane beneath the body. In the latter, synchronous movements of the hindlegs are necessary to avoid rapid spinning in the yaw plane (*1*, *2*).

To reveal the mechanism of this precise synchronization, we made high-speed videos of jumping in nymphs (Fig. 1A) of the planthopper *Issus coleoptratus* (Hemiptera: Fulgoroidea: Issidae) and analyzed the anatomy of the proximal hindleg joints. The most rapid take-off occurred in 2 ms [2.01 ± 0.1 ms (mean ± SEM) for eight nymphs] [supplementary material (SM) and movie S1] with a velocity of 3.9 m/s (mean 2.2 ± 0.56 m/s, n = 8). The two propulsive hindlegs started moving within 30 μs of each other. Such precise synchrony would be difficult to achieve by 1-ms-long neural spikes. The hind coxae are opposed to each other at the ventral midline, and propulsive thrust was generated by large thoracic muscles that rotated

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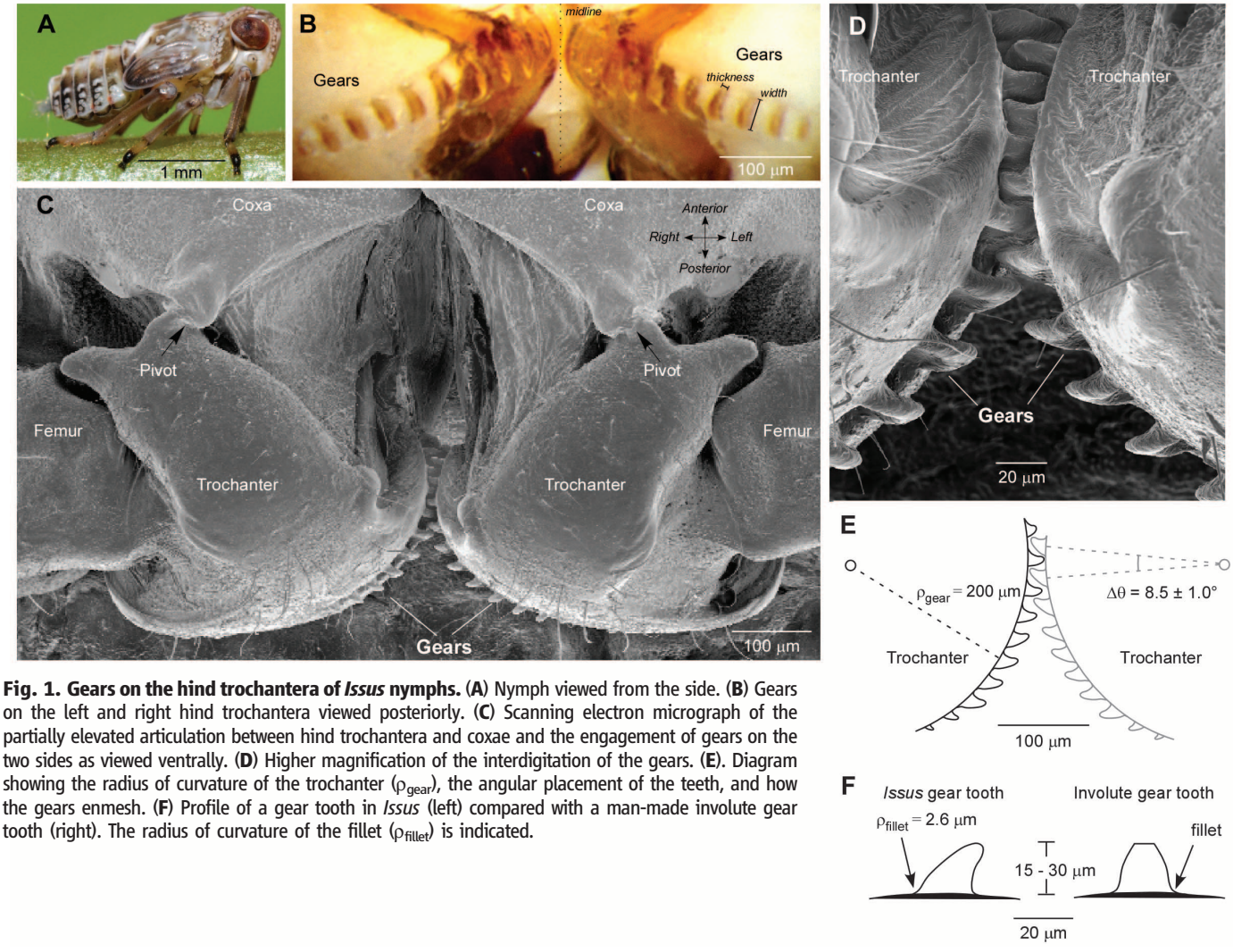


Fig. 1. Gears on the hind trochantera of *Issus* nymphs. (**A**) Nymph viewed from the side. (**B**) Gears on the left and right hind trochantera viewed posteriorly. (**C**) Scanning electron micrograph of the partially elevated articulation between hind trochantera and coxae and the engagement of gears on the two sides as viewed ventrally. (**D**) Higher magnification of the interdigitation of the gears. (**E**). Diagram showing the radius of curvature of the trochanter (ρ_{gear}), the angular placement of the teeth, and how the gears enmesh. (**F**) Profile of a gear tooth in *Issus* (left) compared with a man-made involute gear tooth (right). The radius of curvature of the fillet (ρ_{fillet}) is indicated.

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the trochantera about the coxae. Each hind trochanter of nymphs had a curved strip of gear teeth (Fig. 1B), a feature that extends to other nymphal Fulgoroidea (*3*, *4*). The gear on one trochanter enmeshed with a corresponding gear with teeth of the same size and shape on the other trochanter (Fig. 1, C and D). These gears are not present on the front or middle legs.

Each gear strip was 350 to 400 μm long, contained 10 to 12 teeth, and had a radius of curvature (ρ) of about 200 μm (Fig. 1, E and F). The left and right trochantera had the same number of teeth, which gives a gearing ratio of 1:1. One tooth occurred for every 8.5° ± 1.0° (n = 9 nymphs) of rotation (Fig. 1, D and E). In final instar nymphs, the width of an individual tooth was 80 μm at the anterior end, tapering to 30 μm posteriorly (Fig. 1B). Each tooth was 9 μm thick, was separated from the next tooth by 30 μm, and projected from the surface by 15 to 30 μm, again tapering from the anterior to the posterior end. The dark coloration of the teeth, in contrast with the lighter color of the underlying cuticle, suggests that the teeth are heavily sclerotized (Fig. 1B). Each gear tooth had a curved fillet at its base (Fig. 1E), a feature which, in man-made gears, reduces the likelihood of shearing. In *Issus,* however, the teeth were asymmetric (Fig. 1, D to F), whereas those of man-made gears often have a symmetric shape called an involute designed to work in both rotational directions (*5*). *Issus* gears only have one direction of powered rotation.

To determine the action of the gears in jumping, we captured high-speed images of a nymph restrained on its back but with its legs free. Rapid and synchronous movements of the hindlegs, which have all the characteristics of natural jumps (*6*), could then be induced by gently touching the abdomen. In preparation for a jump, the hindlegs were raised (levated) at their coxo-trochanteral joints so that both hindlegs were rotated forward (*7*) (Fig. 2, A and B; SM; and movie S2). In the propulsive jumping movements, both hindlegs were depressed at the coxo-trochanteral joints with angular velocities as high as 200,000°/s (Fig. 2C, SM, and movie S3). During both the preparatory and propulsive movements, the gear teeth clearly engaged so that both hind trochantera were mechanically constrained to move within 21 μs of each other (Fig. 2, A to C). Two further experiments showed that gears ensure synchronous movements of the hindlegs. First, when the hindlegs were cocked in readiness for jumping, experimental manipulation of the tendon of the large jumping muscle of one hindleg led to the synchronous and rapid movement of the other leg, even in a dead animal. Second, the gears occasionally failed to engage at the start of the propulsive phase of a jump so that some teeth spun past each other. After these few misses, one tooth engaged with a tooth on the other hindleg, which then depressed rapidly, delayed only by a few microseconds relative to the first hindleg. This emphasizes that the gears play a critical role in ensuring close synchrony.

The body mass and measured accelerations predict that the torque generated was about

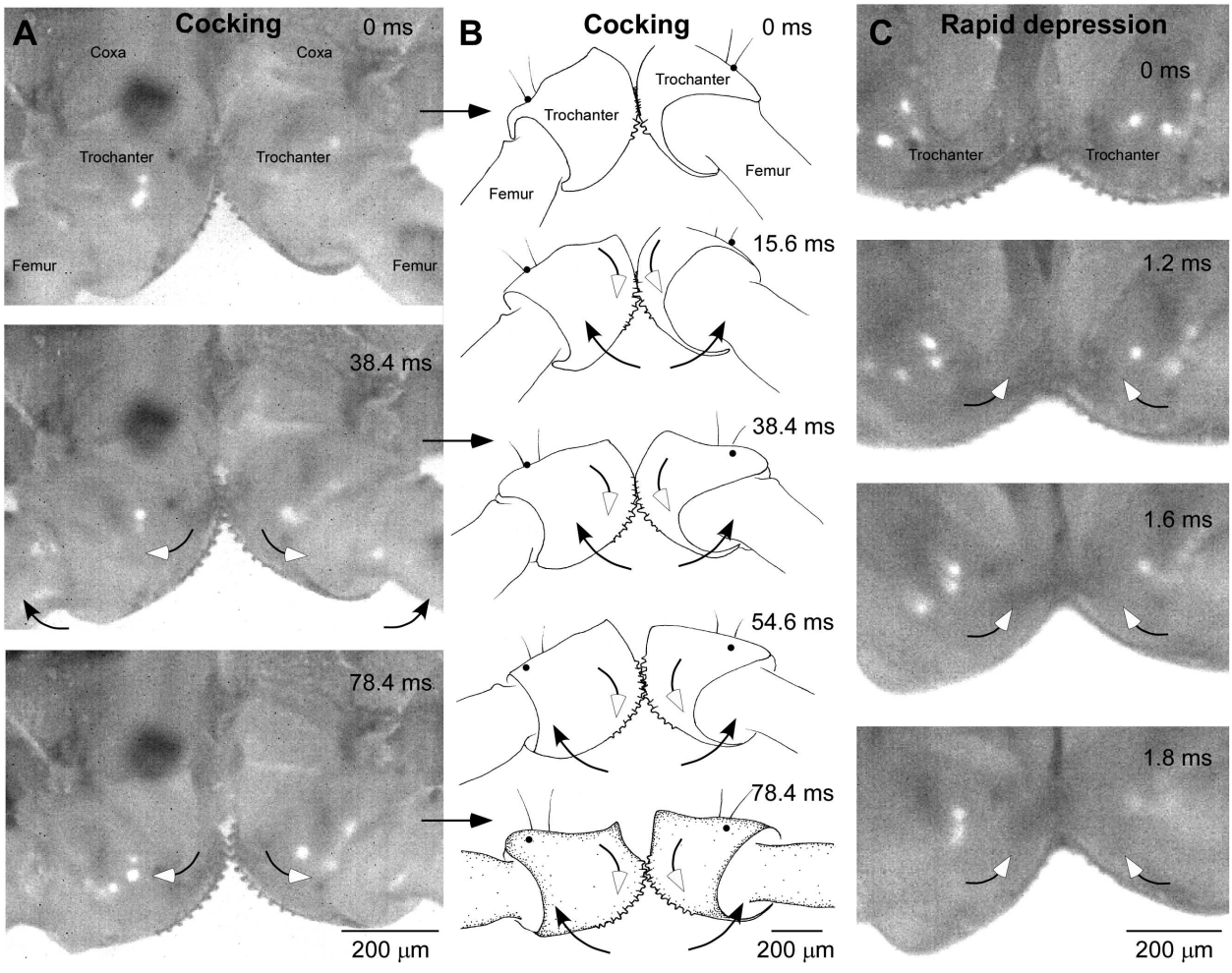


Fig. 2. Engagement of the gears during jumping. (**A**). Three images, at the times indicated (captured at a rate of 5000 images per second) show the levation of the hind trochantera and proximal femora into their cocked position in preparation for a jump (see movie S2). The trochanter starts moving at time 0 ms, and cocking is completed 80 ms later. (**B**) Drawings of the progressive movements of the gears and joints during cocking. The horizontal black arrows indicate the correspondence between the frames in (A) and the drawings. (**C**) Rapid and synchronized depression of the two hindlegs that power jumping (see movie S3). Four images starting from the first detectable depression movement of the hind trochantera (time 0 ms). Full depression was completed 1.8 ms later. The curved, black arrows show the direction of movement of each hindleg and the curved, open arrows, the direction of gear rotation.

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0.7 mN·mm. Each hindleg, and hence each gear, is controlled by separate sets of levator and depressor muscles so that not all the torque goes through each tooth. When one leg moves first at the start of a jump, its gear teeth will engage with and transmit power to the other stationary leg inducing it to move. The left and right power-producing muscles are innervated by independent sets of two motor neurons each, but all four motor neurons carry highly synchronized spike patterns that should help to ensure that the same amount of force is generated in each leg (*7*). This neural mechanism assists the synchrony of the leg movements but cannot deliver the level of synchrony measured during jumping. Thus, the primary role of the gears is to ensure that the hindlegs move synchronously within microseconds of each other.

The gear teeth are lost at the final molt into adulthood. This biomechanically important change in morphology is likely to be triggered by the changed hormonal environment during the larval-to-adult transition (*8*). Adults are, nevertheless, better jumpers than the nymphs; they reach take-off velocities as fast as 5.5 m/s (mean 3.2 ± 0.2 m/s for 10 males) in less than 1 ms (mean 1.5 ± 0.04 ms) and experience forces of 700 *g* (*9*). The adults use frictional contact between the more proximal coxae to ensure synchronous movements of the hindlegs (*1*). Their improved performance may be due to other factors, rather than a consequence of abandoning the gear mechanism. An inherent limitation of gears is that if one tooth breaks, their synchronizing action is degraded. In nymphs, a breakage could be repaired at the next molt, but this is not possible after the final molt to adulthood. Alternatively, the larger size of adults may mean that friction between the trochantera is a more effective synchronization mechanism.

Elsewhere in the animal kingdom, apparently ornamental cogs occur on the shell of the cog wheel turtle *Heosemys spinosa* and on the pronotum of the wheel bug *Arilus cristatus* (Hemiptera, Reduviidae). The hearts of crocodilians have a cog wheel valve (*10*–*12*) that closes during each heart beat and can increase the resistance in the pulmonary outflow (*13*). In some insects, a row of regularly spaced protrusions work like clockwork escapement mechanisms to produce sound (*14*, *15*). In such stridulation mechanisms, a plectrum is moved across the row of teeth (*16*, *17*) at a rate of 2500 to 5000 teeth per second (*16*, *18*), whereas the similarly sized gear teeth of *Issus* spin past each other at almost 50,000 teeth per second. Despite working under very different mechanical conditions, the similar tooth morphologies of the two structures suggest constraints that enforce a particular geometry.

The mechanical gears in *Issus* enhance the synchrony between leg movements to the level of microseconds, so that they are more tightly coupled than most limbed motions. By contrast, but at similar time scales, the parasitoid fly *Ormia ochracea* uses a mechanical linkage to amplify microsecond intra-aural time differences 50 times, so that the azimuth source of sound can be detected more easily (*19*, *20*). The gears in *Issus*, like the screw in the femora of beetles (*21*), demonstrate that mechanisms previously thought only to be used in man-made machines have evolved in nature. Nymphal planthoppers have interacting gears that play an essential functional role in a natural behavior.

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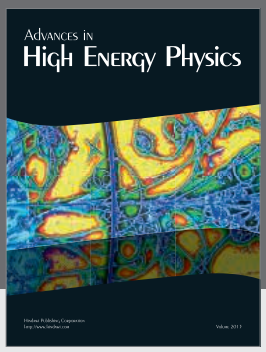
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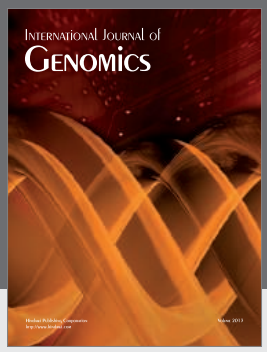
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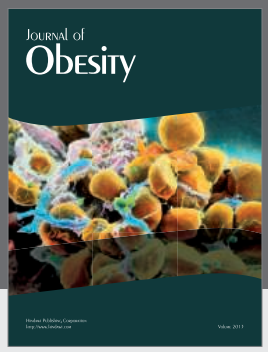
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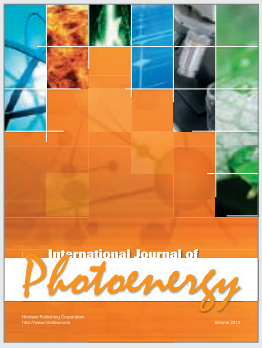


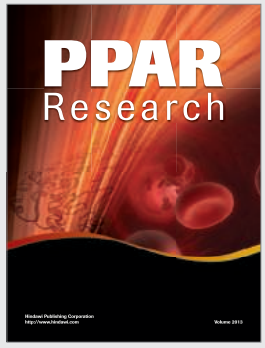




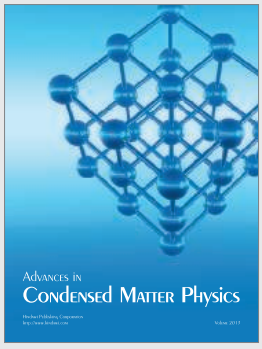


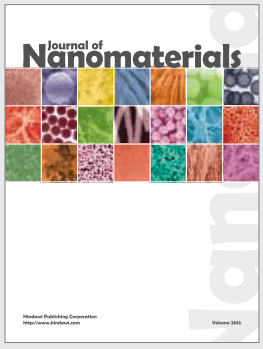




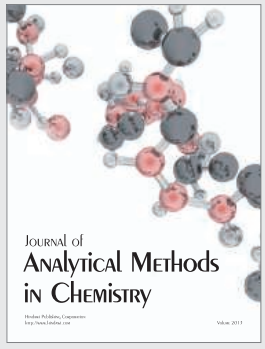


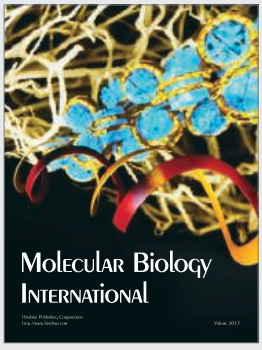


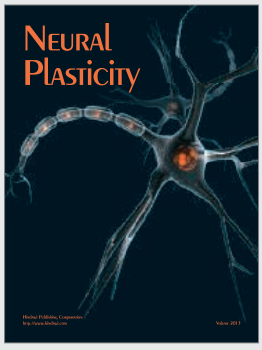


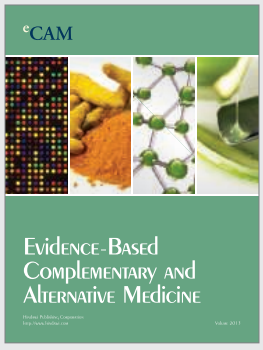


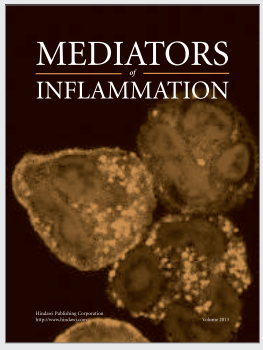


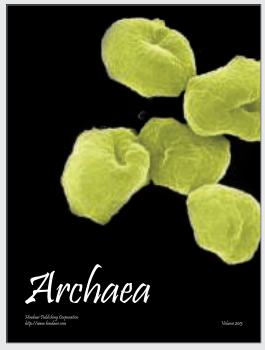












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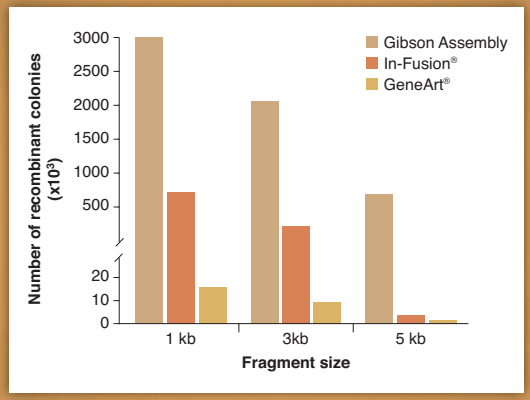
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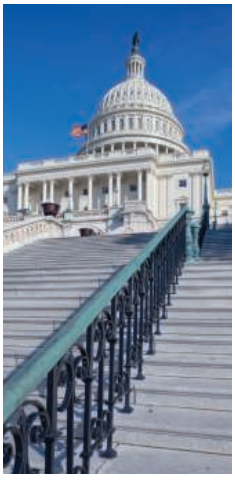


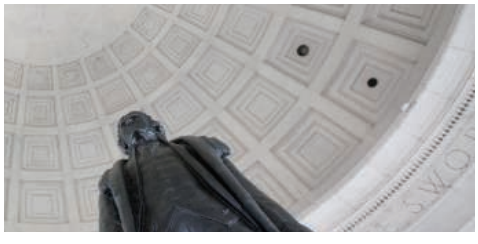
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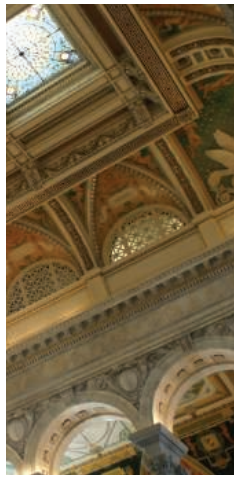


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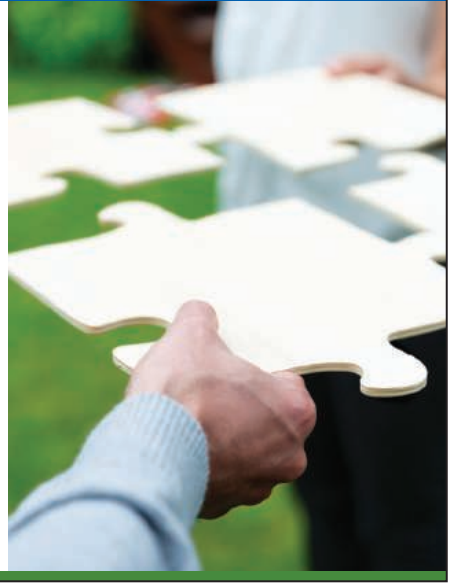
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Navigating Collaborative Grant Research

Marie and Pierre Curie, Watson and Crick, Brin and Page. Collaboration pays, so funding agencies are promoting team research. At the same time, fields that demand multidisciplinary cooperation such as translational medicine, climate science, and systems biology are on the rise. Running a successful collaboration, especially one with several leaders at multiple sites, means thinking like a CEO: vetting partners, delegating responsibilities, and making tough management decisions. Researchers in multisite, multi-investigator projects need to adjust their grant-writing approach, work culture, and even career strategy.

See full story on page 1260.



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Top Employers Survey—October 25

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Winning the Translational Race

Making Good Choices in Biomarker Assay Development for the Clinic

Wednesday, October 9, 2013

12 noon Eastern, 9 a.m. Pacific, 5 p.m. UK, 6 p.m. Central Europe

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- Describe best practices in study design to ensure clinical success of biomarkers
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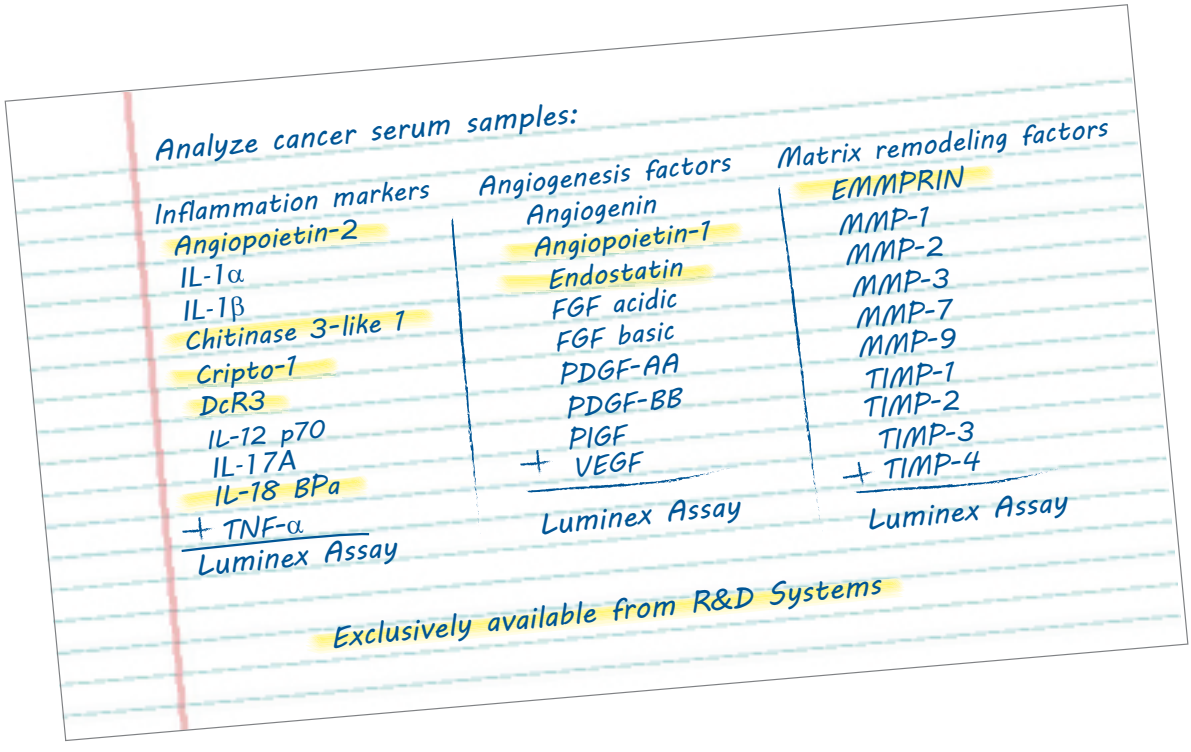
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Applications should be submitted on-line at **http://facultysearches.provost.upenn.edu/postings/23** and include a curriculum vitae, a research statement that includes the candidate's perspective on how she or he fits into one of the core departments, links to no more than three journal publications, and the contact information for three individuals who will provide letters of recommendation. Review of applications will begin **November 1, 2013** and will continue until the position is filled.

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Applicants must apply online at **http://facultysearches.provost.upenn.edu/postings/28**. Required application materials include: curriculum vitae including a list of publications, and a description of proposed research. Applicants should also submit the names and contact information of three individuals who will provide letters of recommendation. Review of applications will begin on **October 14, 2013** and will continue until the position is filled.

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Neurobiology (10-626): The Section of Neurobiology invites applications for a tenure-track position, particularly at the level of Associate Professor with tenure, with a strong research emphasis on molecular and cellular mechanisms of neural circuit development, function, or dysfunction. Candidates using any experimental animal are welcome to apply. The highly interactive Section of Neurobiology at UCSD is looking for a colleague who will bring novel approaches, either technical or conceptual, to their study of brain function. Although not a requirement, candidates who can establish strong ties to the new Center for Brain Activity Mapping initiative at UCSD will be given particular attention.

Plant Biology (10-624): The Section of Cell and Developmental Biology invites applications for a tenure-track faculty position in Plant Biology at the Assistant Professor level. Candidates pursuing innovative research in areas including, but not limited to, signaling, metabolism, growth and development, cell biology, plant-microbe interactions, natural variation, and comparative and quantitative genomics are encouraged to apply.

Quantitative Evolutionary Biology (10-629 and 10-628): The Section of Ecology, Behavior and Evolution invites applications for two faculty positions in Quantitative Evolutionary Biology, one at the Associate or full Professor level with tenure (10-629) and another at the tenure-track Assistant Professor level (10-628). We are searching broadly for evolutionary biologists with strong quantitative skills working with any taxonomic group (animal, plant, microbial) or environment (terrestrial or aquatic). Research interests may include, but are not limited to: evolutionary theory and modeling; investigation of how genetic variation affects complex traits and their evolution; experimental evolution; and/or the use of genomic tools and comparative analysis to reconstruct the evolutionary histories of populations and species; with the goal of understanding how traits evolve under different kinds of selection, including those associated with global change. Both positions are part of a campus-wide initiative for growth in the areas of Systems and Quantitative Biology (qBio).

Review of applications will commence by **October 15, 2013** and will continue until all the positions are filled. Interested applicants must submit a cover letter, curriculum vitae, statement of research, statement of teaching, a statement describing their past experience and leadership in fostering equity and diversity and/or their potential to make future contributions, 3-5 publications, and 3-5 references. Applications must be submitted through the University of California San Diego's Academic Personnel RECRUIT System at **https://apolrecruit.ucsd.edu/apply**. To view the full postings visit: **http://biology.ucsd.edu/jobs/faculty.html**.

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Navigating Collaborative Grant Research



Marie and Pierre Curie, Watson and Crick, Brin and Page. Collaboration pays, so funding agencies are promoting team research. At the same time, fields that demand multidisciplinary cooperation such as translational medicine, climate science, and systems biology are on the rise. Running a successful collaboration, especially one with several leaders at multiple sites, means thinking like a CEO: vetting partners, delegating responsibilities, and making tough management decisions. Researchers in multisite, multi-investigator projects need to adjust their grant-writing approach, work culture, and even career strategy. **By Chris Tachibana**



Mark Gerstein

Scientific collaborations can be as casual as swapping ideas over coffee; they can be as monumental as the Manhattan Project, the Large Hadron Collider, or the Human Genome Project. They are increasingly how we do science. Around the world, funding agencies are emphasizing collaborations for many reasons—most, of course, financial.

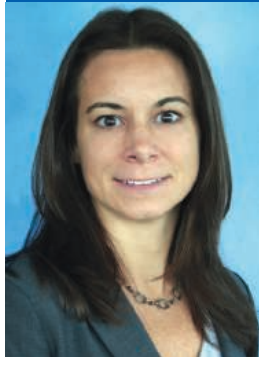
"Resources are shrinking," says **Alicia Knoedler,** associate vice president for research, University of Oklahoma. "So government, industry, and some private funders prefer a collaborative approach." Getting experts to work together on a problem can be more effective than supporting many separate projects. Sharing equipment in core facilities avoids duplication and reduces maintenance. Many funding agencies want to see commercialization of research discoveries and translation of results into clinical practice, which requires crossdisciplinary work. For example, the Health Care Systems Research Collaboratory, which received $11.3 million in 2012 from the National Institutes of Health (NIH) Common Fund, is supporting research partnerships between academic scientists and health care systems to improve clinical practice. **Michael Katze,** University of Washington microbiology professor and lead investigator for collaborative NIH programs that use systems biology approaches to investigate viral-host interactions, puts it bluntly: "The NIH is impatient with basic science," he says. "They want a shorter drive to vaccines and other applications."

Actually, the NIH, which created a multiple principal investigator (PI) option only in 2006, is a bit late to the game. The National Science Foundation (NSF) has a longer history of collaborative science models, beginning with its Engineering Research Centers in the 1980s. Knoedler says the NSF is still a leader in funding interdisciplinary collaborations, with the Science and Technology Centers and the Industry & University Cooperative Research Program. Other U.S. government-funded research consortia include the Department of Energy (DOE) Innovation Hubs and Energy Frontier Research Centers, and the Department of the Interior Regional Climate Centers. The National Network for Manufacturing Innovation has funding through the DOE and Department of Defense to move innovations, for example in biotechnology or nanotechnology, to market. And the new brain initiative could bring more collaborative opportunities, possibly as NIH program project grants.

NIH program project grants fund investigators who are working on related projects that draw on shared resources. An example is the $20 million supporting the Breast Cancer Surveillance Consortium (BCSC). The BCSC collects longitudinal data from several mammography sites nationwide, with information on over 10 million mammograms so far. These and other data are used to study breast cancer risk factors and the effectiveness of breast cancer screening, diagnosis, and treatment. Centralized administrative cores increase efficiency and BCSC communication channels enhance research. "The science is improved from the synergy created by working together instead of independently," says **Diana Miglioretti,** Dean's professor of biostatistics, University of California Davis School of Medicine; senior investigator, Group Health Research continued>

"Resources are shrinking. So government, industry, and some private funders prefer a collaborative approach."
—Alicia Knoedler

Diana Miglioretti



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Regional Focus: China—November 15



GENOME VARIATION | CELLULAR BIOPHYSICS | SYNTHETIC BIOLOGY

Are you a creative investigator who excels at working collaboratively and pushing disciplinary boundaries?

Then we want to hear from you. The College of Biological Sciences at the University of Minnesota is hiring scientists for **three interdisciplinary research clusters in emerging areas of biology: genome variation, cellular biophysics and synthetic biology.** All positions are tenure track. Successful candidates will have expertise that complements current faculty and be committed to graduate and undergraduate education.

Learn more about research themes and specific positions at the college's cluster hiring website.

z.umn.edu/cbsclusterhiring

College of Biological Sciences
University of Minnesota
Driven to Discover℠



"Allow extra time for editing since many different specialists are involved. And have an independent reviewer read the proposal to make sure it reads as a unified whole and not a collection of individual projects."
—Peter Larsen

Institute; and BCSC co-PI. But programs like the BCSC aren't built in a day. That's why development experts say the first step of collaborative science is assembling a research team.

Strong Relationships

"My most important advice about collaborations," says Knoedler, "is to build strong research relationships in advance." All collaborators must know they are crucial members of the research team or they'll drop the ball or drop out. And tokenism shows in a proposal, says Knoedler. "It's obvious to reviewers when people have just been placed on a team and not integrated into it."

Creating a functional crossdisciplinary research team requires serious vetting. Choose senior investigators because agencies tend to fund people with an established record. Look for team players. Katze selects collaborators who are experts in their field and people he can count on to deliver results that integrate into the overall project goals. Establish real, meaningful collaborations, he says. Don't include people just to check off grant requirements.

Ruedi Aebersold agrees, saying his most effective collaborations have been with tight, focused teams on time-limited projects. Aebersold, a professor at the ETH (Swiss Federal Institute of Technology), is the founding executive of Systemsx.ch, a partnership of 12 Swiss universities and research institutions that funds interdisciplinary systems biology projects. Like Katze, Aebersold transitioned from single-laboratory to multi-investigator work when, in the late 1990s, the doubling of the NIH budget coincided with the rise of systems biology, a data-driven field that brings together biologists, computer programmers, bioengineers, and statisticians. From 2002 to 2009, Aebersold was the PI of an NIH center grant to develop proteomic technology. Based on its success, his advice is: "Resist the urge to be expansive." If you include all possible collaborators you'll create a bloated, unproductive team and as PI, you'll be in the uncomfortable position of needing to cut people later.

In fact, Aebersold and other scientists bemoan collaborative European Union (EU) grants that almost demand inclusion of partners from specific sectors, such as small business, and geographic regions, such as countries without a strong research infrastructure. These mechanisms reflect the EU mission of economic growth, stability, and social cohesion among members. "But instead of sprinkling money around," says Aebersold, "the most efficient collaborations focus a lot of money on a few groups." A laboratory that receives a substantial chunk of funds will make the project a high priority, says Aebersold, who says a good example of funding small teams of committed researchers is the Synergy Grants.

Agnes Kulcsar is the call coordinator for the European Research Council (ERC) Synergy Grants. The ERC is the EU's arm for funding investigator-driven projects and in 2012, the ERC Scientific Council established the multi-investigator Synergy Grant program. The goal, says Kulcsar, is "encouraging a small group of researchers to jointly address challenging and interdisciplinary research and unconventional approaches, to see what breakthroughs or even new fields of research emerge." To meet this broad goal, the proposals are flexible in project size, topic, and team composition—with no trans-nationality requirements. Projects funded so far range from the humanities to quantum physics to clinical science. After the current round of proposals is reviewed and funded, the program's value will be evaluated in early 2014.

Kulcsar reinforces the importance of the research team. The most important criterion for Synergy Grants, she says, is showing that "everything has come together—the right challenge and strong scientific partners with fully complementary expertise working on a project that only these people can do, and only at this time." The common factor in all the successful applications so far, says Kulcsar, is a sense of unity and exciting science. That excitement comes from careful, meticulous planning.

Diversity and Unity

Once you have your research dream team, set ground rules, says **Barry Bozeman,** an Arizona State University professor of public policy who is studying the dos and don'ts of collaborations for the NSF. "People focus on getting the money and don't worry about other issues until it's too late," he says. "Intersector work can be fraught with misunderstanding and managing a heterodox team is hard." Scientific disciplines differ in their norms about authorship and credit, work culture, and expectations about intellectual property rights and distribution of results. Discuss those issues in advance, says Bozeman. The decision-making process and the budget should be clear as well as the division of labor and timelines, he says. "Let people know what they are expected to do and when."

Your team needs money, so to find funding, **Peter Larsen,** director of research development at Michigan Technological University recommends networking with funding agency program officers and signing up for alerts from relevant agencies. Search in funding databases such as Pivot, SciVal Funding, or Grant Forward, which require an institutional subscription, or free databases like Grants.gov. Knoedler suggests using keywords such as "center," "hub," and "regional." Focusing on limited submission opportunities can find an agency's most high-profile and likely collaborative proposal calls.

Next, write a focused, concise proposal. Grant development experts such as Knoedler and Larsen say that writing collaborative proposals requires exponentially more time and a different mindset than writing a single-project grant. You must highlight the diverse expertise of your team while conveying commitment to a common goal. For NSF grants, you must demonstrate a broad impact on society. "Allow extra time for editing," says Larsen, "since many different specialists are involved. And have an independent reviewer read the proposal to make sure it reads as a unified whole and not a collection of individual projects." Finding a reader who is not on the team and not a potential competitor or reviewer can be difficult, but networking through your institution's development office can help. Reviewers are looking for excellence in the research, not buzzwords, says Kulcsar. She says continued>

CREDIT: MICHIGAN TECH PHOTO

EMBL

The European Molecular Biology Laboratory is searching for Group and Team Leaders. EMBL offers a highly collaborative, uniquely international culture. It fosters top quality, interdisciplinary research by promoting a vibrant environment consisting of young, independent researchers with access to outstanding graduate students and postdoctoral fellows. EMBL is an inclusive, equal opportunity employer offering attractive conditions and benefits appropriate to an international research organisation.

Group and Team Leader Opportunities

GENOME BIOLOGY

at EMBL Heidelberg, Germany

The Genome Biology Unit studies the molecular mechanisms by which genetic information is expressed and regulated to yield complex biological systems, and how genetic variation leads to phenotypic diversity. The Unit addresses questions at different scales, ranging from detailed mechanistic studies (using genetics, chemistry, biochemistry and microfluidics) to genome-wide studies (using functional genomic, proteomic and computational approaches). This powerful combination enables the unit to dissect and model complex processes going from genotype to phenotype.

This **Group Leader** position provides a very competitive package to support an independent research group in an excellent scientific and highly collaborative environment. We particularly encourage candidates applying a systems biology approach to understanding specific aspects of gene expression regulation, evolution, metabolomics, stem cell biology or genomic applications to health to apply, but welcome candidates with demonstrated excellence in any area of genome biology.

Further information about the position can be obtained from the Head of Unit, Eileen Furlong (**eileen.furlong@embl.de**).

Interviews are planned for 25, 26 and 27 November 2013.

COMPUTATIONAL BIOLOGY/ BIOINFORMATICS

at EMBL Heidelberg, Germany

Bioinformatics activities are integral to the interdisciplinary research activities at EMBL and thus we seek to recruit an outstanding **Group or Team Leader**, working in the broad area of computational biology and bioinformatics, who would utilise the highly interdisciplinary and collaborative environment at EMBL Heidelberg.

Our search for candidates is deliberately broad and comprises all areas of computational biology that are complementary and synergistic to existing research activities at EMBL Heidelberg. Possible research areas comprise but are not limited to structural bioinformatics (e.g. modelling of protein complexes and their interactions and/or dynamics in a cellular context), image analysis/visualisation (e.g. reading out data from GFP screens, E-tomograms or visualising a virtual cell atlas), cheminformatics (e.g. chemical-protein-network analysis), systems bioinformatics (e.g. tissue modelling, analysis network perturbations) or transcriptional regulation/epigenetics (e.g. chromatin modification analysis).

We are open to applications from candidates who wish to focus entirely on their own research projects and, because there is an increasing need to integrate and streamline the multiple computational approaches followed within EMBL, to candidates who wish to function at the interface between research and service activities.

For further information about this position please contact **recruitment@embl.org**.

Interviews are planned for 9, 10 and 11 December 2013.

STRUCTURAL BIOLOGY OF COMPLEXES

at EMBL Grenoble, France

The appointed **Group Leader** will be an ambitious structural biologist with an original multidisciplinary research programme oriented towards structure-function relationships of macromolecular complexes in eukaryotic systems. Particular, but not exclusive, areas of interest are host-pathogen interactions, RNA biology or computational biology/modelling. He/she will benefit from the world-class environment of the EMBL Grenoble Outstation within the Partnership for Structural Biology (www.psb-grenoble.eu) which gives access to integrated state-of-the-art structural biology technologies, including ESRF synchrotron X-ray beamlines for MX and SAXS, cryo-EM/tomography and NMR as well as protein expression screening, insect cell, biophysics, confocal microscopy and high-throughput crystallization platforms.

Applicants should have a Ph.D. and at least 3 years post-doctoral experience and a strong record of achievement in structural, molecular or cell biology.

Further information about the position can be obtained from the Head of Grenoble Outstation, Stephen Cusack (**cusack@embl.fr**).

Interviews are planned for 2, 3 and 4 December 2013.

APPLICATION INSTRUCTIONS

Please apply online through **www.embl.org/jobs** and include a cover letter, CV and a concise description of research interests and future research plans. Please also arrange for 3 letters of recommendation to be emailed to **references@embl.de** at the latest by 20 October 2013.

Further information on Group/Team Leader appointments can be found under **www.embl.org/gl_faq**.

For more information please visit:

www.embl.org

Featured Participants	Additional Resources
Arizona State University www.asu.edu	**European Research Council Synergy Grants** erc.europa.eu/funding-schemes/synergy-grants
Breast Cancer Surveillance Consortium breastscreening.cancer.gov	**Grant Forward** www.grantforward.com/index
ETH www.ethz.ch/index_EN	**Grants.gov** www.grants.gov
European Research Council erc.europa.eu	**National Institutes of Health: Multiple Principal Investigators** www.grants.nih.gov/grants/multi_PI
Group Health Research Institute www.grouphealthresearch.org	**National Organization of Research Development Professionals** www.nordp.org/funding-opportunities
Michigan Technological University www.mtu.edu	**National Science Foundation** www.nsf.gov
University of California Davis www.ucdavis.edu	**Pivot** pivot.cos.com
University of Oklahoma www.ou.edu	**SciVal Funding** www.funding.scival.com
University of Washington www.washington.edu	
Yale University www.yale.edu	



The goal is "encouraging a small group of researchers to jointly address challenging and interdisciplinary research and unconventional approaches, to see what breakthroughs or even new fields of research emerge." —Agnes Kulcsar

that at the ERC, reviewers want to feel that "no matter what, it will be interesting to see what comes out of the project. Even if it is not exactly what is planned, something groundbreaking will result from this collaboration."

Kulcsar and Aebersold both say that professional EU grant consulting companies are not necessary. Although these companies help navigate the exceedingly complex EU applications, says Aebersold, universities and research institutions often have their own experts who can help, saving the expense and time demands of outside consultants. However, if your university or institution does not have the infrastructure and personnel to manage large, multisite grants, start hiring. You simply must have a project manager to guide proposal development and herd the various PIs once you get funded. Knoedler says, "You're foolish if you don't. In fact, if you don't write a manager into your grant, it's a sign to reviewers that you don't know what you're doing." However, scientists are often reluctant to spend money on a manager.

Well, most scientists. The Katze group has so many collaborative grants involving hundreds of people that it has its own administrative hub for finances, writing, and administration. **Lynn Law,** a research scientist in the Katze group, moved from doing bench science to managing collaborative projects. "I hold people accountable, get everybody on same page, and make sure they have same goals," she says. "The PIs that Michael brings in are used to being their own bosses so working as team doesn't always come easily to them." Many scientists have poor management skills, says Katze, but these skills are essential to running big collaborative projects. His advice: "Learn to delegate, trust people, and don't micromanage them. Let them grow into their job."

Success at large collaborative projects, says Katze, requires being good at all the things scientists are often bad at. "You have to be outgoing and entrepreneurial and take risks," he says. "As the PI, if people don't come through, you have to make hard decisions and cut them from the project." Katze trains his students and postdocs to be collaborators and leaders of multi-investigator projects. But most of the scientific world is still adjusting to collaborative science, especially when evaluating people for hiring, promotion, and tenure.

Collaborations and Careers

Early career scientists considering a multi-investigator project should weigh the experience, networking opportunities, and prestige of a high-profile national or international collaboration against the disadvantages. For example, being on a multiple-PI grant could affect NIH New Investigator status, which gives special consideration to researchers applying for funding if they have not previously received major NIH grants. Another disadvantage is being author number 53 in publications from the project, since first authorship is used to evaluate job and tenure candidates. Says Aebersold, "Personally, I value someone who can operate in a collaborative environment, but when we advertise for a position, we get hundreds of applications. It's flawed, but we focus on first authorship because it's hard to evaluate contribution to a consortium."

But **Mark Gerstein** has a collaborative career strategy. Among other initiatives, his group contributes to ENCODE (Encyclopedia of DNA Elements), supported by NIH to define functional genomic elements; the DOE Systems Biology Knowledgebase (KBase) for data sharing and analysis; and the internationally funded 1000 Genomes Project on human genetic variation. "I'm used to being a cog in a big machine," says Gerstein, a professor of biomedical informatics and computer science atYale University. Collaborating, he says, lets him contribute to research that has a greater impact than single-laboratory studies. Gerstein recognizes that this work doesn't fit in the tenure-track groove, though. "Most universities expect you to bring in your own money and publish your own papers, so I do that as well." Gerstein first puts students and postdocs in his lab on large collaborations, then gives them smaller follow-up projects for their own first-author papers. This strategy has placed lab members in faculty positions around the world. Early career scientists should also keep department chairs, deans, and other administrators informed about their participation in large collaborations so those contributions are recognized and valued.

Collaboration has pros and cons, says Gerstein. "Sometimes you have to wait to publish until the consortium is ready, and you can't always do things the way you want to. But the benefit is being on high-impact publications and highly connected work. For these projects," he says, "the whole is greater than the sum of the parts, and I've profited from being part of the whole."

Chris Tachibana is a science writer based in Seattle, USA and Copenhagen, Denmark, and is a part-time employee of Group Health Research Institute.

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CREDIT: COURTESY OF AGNES KULCSAR

EXCITING FACULTY OPPORTUNITIES IN CENTRAL MASSACHUSETTS

WPI

BIOINFORMATICS
Worcester Polytechnic Institute
Tenure Track (Open Rank)

WPI invites applications for a tenure track (open rank) Professor position with a research focus in Bioinformatics to begin in the fall of 2014. The successful candidate will hold an academic appointment within Biology and Biotechnology, Computer Sciences, or Mathematical Sciences. Supported by the Life Sciences and Bioengineering Center (LSBC) at Gateway Park, a state-of-the-art, interdisciplinary research facility, WPI is committed to further strengthening its capabilities in the Life Sciences arena. With the exceptional research environment at the LSBC, the successful candidate is expected to develop a robust, externally funded, high profile research program in bioinformatics or computational biology. Applicants should have a Ph.D. in Bioinformatics, Computer Sciences, Biology, Statistics, Mathematics, or a related area, and significant postdoctoral research experience. Resources for startup funding are competitive and commensurate with research experience and accomplishments.

Founded in 1865, WPI is one of the nation's first technological universities. A highly selective private university located within an hour of Boston, WPI is consistently ranked among the top 60 research institutions by US News & World Report. The university is home to an innovative and intensive project-based curriculum that empowers students with the knowledge and skills to address real world problems around the globe, an approach repeatedly cited for excellence by The Fiske Guide to Colleges and The Princeton Review. WPI offers exceptional teaching and research opportunities, as well as opportunities for affiliate appointment and collaboration with our colleagues at the University of Massachusetts Medical School.

Applicants are asked to apply electronically by visiting Careers at WPI; **https://careers.wpi.edu/**. Review of applications will be conducted on a rolling basis and continue until the position is filled. To learn more about WPI, please visit **http://www.wpi.edu/academics**.

To enrich education through diversity, WPI is an Affirmative Action, Equal Opportunity Employer.

UMASS

University of Massachusetts Medical School
Program in Bioinformatics and Integrative Biology

The Program in Bioinformatics and Integrative Biology at University of Massachusetts (UMASS) Medical School invites applications for **tenure-track or senior tenured professor positions**. We are seeking innovative, energetic and collaborative individuals who plan to develop strong computational research programs to tackle problems in one of the following areas: regulatory genomics, comparative genomics, systems biology, RNA biology, evolutionary biology, statistical genetics, or proteomics. Exceptionally strong candidates in other computational biology areas will also be considered. Wet bench research space can be arranged for individuals who are interested in performing experiments to augment their computational efforts.

The Program in Bioinformatics and Integrative Biology is housed in the new state-of-the-art Albert Sherman building next to Program in Systems Biology and the RNA Therapeutics Institute. Closely collaborating Program in Gene Function and Expression, Program in Molecular Medicine, and Department of Biochemistry and Molecular Pharmacology are located in neighboring buildings. The Program is supported by high-performance computing facilities. Salary and start-up package will be highly competitive and commensurate with the high level of accomplishment expected of successful applicants.

Applicants should submit a cover letter explaining their interest in the Program, a curriculum vitae that includes publications, honors, and a succinct research plan to **http://www.academicjobsonline.org** (Position ID# 2879). To expedite the review process, applicants should invite three individuals who are familiar with your work and potential for success to upload their recommendation letters at the same web address. Review of applications will begin on November 1, 2013 and continue until positions are filled. Inquiries, but not application materials, may be directed to Professor Zhiping Weng at **zhiping.weng@ umassmed.edu.**

UMASS Medical School has built a reputation as a world-class research institution in basic and clinical Research. The Medical School attracts more than $250 million in research funding annually, 80% of which comes from federal funding sources. The Medical School is located within a ten-minute drive from Worcester Polytechnic Institute (WPI). The two Universities have numerous joint research and educational efforts in Bioinformatics and Systems Biology.

As an Equal Opportunity and Affirmative Action Employer, UMMS recognizes the power of a diverse community and encourages applications from individuals with varied experiences, perspectives and backgrounds.

UMASS University of Massachusetts Medical School

PROGRAM IN SYSTEMS BIOLOGY

Faculty Positions
Program in Systems Biology

The newly established Program in Systems Biology invites applications from outstanding candidates for a **tenure-track or senior tenured professor position**. Rank will be commensurate with ability and experience. The positions will be highly competitive with regard to start-up funds, laboratory space and salary.

The candidate will be expected to develop and maintain an innovative, externally funded research program. We are seeking energetic and collaborative individuals who will develop a strong research program to tackle important problems in one of the following areas in systems biology: Network Biology, Single Cell Systems Biology, Genome Biology, Evolution and Variation. Exceptionally strong candidates in other areas will also be considered.

The Program in Systems Biology is housed in the new Albert Sherman Center that opened early in 2013. The Program has high-performance computing facilities, state-of-the-art laboratory space and equipment and a full-time systems administrator to support the research activities of its Faculty. Further information on the Program can be found at **www.umassmed.edu/psb**.

Applicants should submit a cover letter explaining their interest in the Program, a curriculum vitae that includes honors, publications, and a succinct research plan to **http://www.academicjobsonline.org** (Position ID# 2970). The position is open until filled. To expedite the review process, applicants should invite three individuals who are familiar with their work and potential for success to upload their recommendation letters at the same web address. Inquiries, but not application materials, may be directed to **Professors A.J. Marian Walhout (marian.walhout@umassmed.edu)** or **Job Dekker (job.dekker@umassmed.edu)**.

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Science Careers online @sciencecareers.org
FACULTY POSITIONS

PENNSTATE HERSHEY College of Medicine

FACULTY POSITION IN BIOCHEMISTRY, MOLECULAR BIOLOGY, AND GENETICS

The Department of Biochemistry and Molecular Biology at the Penn State University College of Medicine is expanding under the new leadership of Dr. James R. Broach. The Department invites applications from outstanding scientists with Ph.D., M.D., or equivalent degrees for a full-time tenure-track position. We seek candidates at the Assistant Professor level who have an active highly competitive independent research program or who show a strong potential to develop such a program. We are looking for candidates in the areas of molecular biology, genetics, epigenetics, and/or genomics. Candidates will have the opportunity to participate in Penn State's medical genomics program through the new Institute for Personalized Medicine. For additional information, please visit the following website: **http://www2.med.psu.edu/biochemistry/**. Applicants should submit a curriculum vitae and a brief statement of research plans, and arrange for three letters of reference to be sent to **Faculty Search Committee, biochem_apply@hmc.psu.edu or to Department of Biochemistry and Molecular Biology H171, Penn State University College of Medicine, Hershey PA 17033**. Application should be received prior to **November 15, 2013**.

Penn State is committed to Affirmative Action, Equal Opportunity and the diversity of its workforce.

NORTHWESTERN UNIVERSITY

ASSISTANT PROFESSOR

The Department of Molecular BioSciences encourages outstanding individuals with research interests that complement existing strengths of the department to apply for tenure-track appointments at the level of **Assistant Professor**. The department is an exciting interdisciplinary research and training environment located on Northwestern's Evanston, Illinois campus (**http://www.molbiosci.northwestern.edu**). Current faculty research interests encompass biochemistry, cell and developmental biology, structural biology and molecular biology.

We are particularly interested in the following areas:

- Biophysical approaches to study protein structure and function including protein-protein or protein-nucleic acid interactions.
- Structural biology that includes the use of cryoelectron microscopy.

Applicants should prepare a cover letter, curriculum vitae, statement of teaching experience and interests, research summary, and a statement of future research goals. For further instructions and to submit an application, please visit the Molecular BioSciences homepage at **http://www.molbiosci .northwestern.edu**. Applicants should arrange for at least three letters of recommendation to be submitted on their behalf. Questions should be sent to molbioscisearch@northwestern.edu.

To ensure full consideration, please submit all materials by **November 1, 2013**.

Northwestern University is an Affirmative Action/Equal Opportunity Employer. Women and underrepresented minorities are especially encouraged to apply.

Molecular, Cellular, & Developmental Biology Faculty Search

UNIVERSITY OF MICHIGAN FACULTY POSITIONS IN MOLECULAR, CELLULAR, AND DEVELOPMENTAL BIOLOGY

The Department of Molecular, Cellular, and Developmental Biology in the College of Literature, Science and the Arts at the University of Michigan solicits applications for faculty positions at the assistant professor level, but appointment at a more senior level is possible for applicants with suitable experience. The faculty position will be tenured or tenure track with a university year appointment starting September 1, 2014 or January 1, 2015. Successful candidates will be expected to establish a vigorous, extramurally funded research program and to be involved in instruction of both undergraduate and graduate students.

We welcome applications from outstanding biologists in any area of research within the scope of the department, which includes studies of model organisms (plants, animals, and microbes) with a variety of approaches (genetics and genomics, biochemistry and structural biology, molecular biology, cell and developmental biology, and physiology). We particularly encourage applications from neuroscientists who use genetic, cellular and/or molecular approaches. For further information about Department research areas, please visit **www.lsa.umich.edu/mcdb**.

All applications must be submitted on-line at **http://labs.mcdb.lsa.umich.edu/search13**. You will be asked to upload the following materials: A cover letter, a *curriculum vitae*, a brief summary of recent research accomplishments and statement of future research plans, a statement of teaching interests and philosophy, and evidence of teaching excellence for those who have teaching experience. Candidates for appointment as an assistant professor should provide names and contact information for at least three references, as instructed in the on-line application form. To ensure full consideration, all materials should be received by **October 13, 2013**.

Women and underrepresented minorities are encouraged to apply. The University of Michigan is supportive of the needs of dual career couples and is an Equal Opportunity/Affirmative Action Employer.

UT SOUTHWESTERN MEDICAL CENTER

Assistant Professor in Human Genetics

The Center for Human Genetics (McDermott Center for Human Growth & Development) at UT Southwestern Medical Center (**http://www.utsouthwestern.edu/education/medical-school/departments/mcdermott-center/index.html**) invites applications for a tenure-track position of Assistant Professor. We are seeking individuals with innovative experimental research programs in human molecular genetics. Successful applicants will be expected to establish a vigorous independent research program and to teach students at the graduate level.

The individual should hold a graduate degree (MD, PhD or MD/PhD) and have completed a post-doctoral fellowship or be a candidate for the NIH Director's Early Independence Award. The appointment will include a competitive salary, attractive start-up package, excellent laboratory space in a dynamic research environment with access to the Center's state-of-the-art infrastructure for basic and clinical research related to human genetics, including family/patient collection, genetic variation, next-generation sequencing and bioinformatics cores. The faculty member will be jointly appointed to a basic science or clinical department. Applicants should submit their curriculum vitae containing a summary of past accomplishments, a statement of future objectives, and three professional references by email to:

Faculty Search Committee
c/o Susan Hayes, Dept. Administrator
McDermott Center for Human Growth & Development
UT Southwestern Medical Center
5323 Harry Hines Boulevard
Dallas, Texas 75390-8591
Susan.Hayes@UTSouthwestern.edu

UT Southwestern Medical Center is an Affirmative Action/Equal Opportunity Employer. Women, minorities, veterans and individuals with disabilities are encouraged to apply.

Science Careers online @sciencecareers.org
FACULTY POSITIONS

Berkeley
University of California

Department of Molecular and Cell Biology

The Department of Molecular and Cell Biology (MCB) is seeking applications for four faculty positions in the areas listed below. We seek candidates with Ph. D. and/or M.D. degree who have demonstrated excellence, originality and productivity in research, and interest in undergraduate and graduate teaching. Ph.D. or equivalent is required by date of hire.

Applications should include a *curriculum vitae*; a list of publications; copies of three significant publications; a brief description of research accomplishments; and a statement of research objectives and teaching interests. We are particularly interested in candidates who will contribute to diversity and equal opportunity in higher education through their teaching, research, and service; candidates are invited to address this issue in their application. Applicants for the tenure level in the Biology of Cancer or Emerging & Neglected Diseases searches should include a list of five references with their application; letters of reference are not required at this time. Applicants for the Assistant professor level positions should arrange to have three letters of reference submitted online. All letters will be treated as confidential per University of California policy and California state law. Please refer potential referees, including when letters are provided via a third party (i.e., dossier service or career center), to the UC Berkeley statement of confidentiality (http://apo.chance.berkeley.edu/evalltr.html) prior to submitting their letters.

The deadline for applications is October 31, 2013.

UC Berkeley is committed to addressing the family needs of faculty. Women and minority candidates are especially encouraged to apply. The University of California is an Affirmative Action/Equal Opportunity Employer.

Systems Developmental Biology
We seek candidates whose research focuses on the use of systems-level technologies (e.g., advanced imaging methods, whole-genome analysis, computational modeling) to understand developmental processes (e.g. live imaging of cell migration, gene activity) in either invertebrates or vertebrates. This position is open at the Assistant Professor level (tenure-track). *Applications should be submitted online through https://aprecruit.berkeley.edu/apply/JPF00214. See above application details.*

Molecular, Cellular, and Developmental Neurobiology
We seek candidates who use cellular/molecular, optical, biophysical and/or neurophysiological approaches to study neurons,neuronal signaling, synapses, brain circuits, neural development or disease. However, all areas of neuroscience will be considered. The successful candidate will also join the Helen Wills Neuroscience Institute (http://neuroscience.berkeley.edu). This position is open at the Assistant Professor level (tenure-track). *Applications should be submitted online through https://aprecruit.berkeley.edu/apply/JPF00215. See above application details.*

Biology of Cancer
We seek candidates interested in the mechanisms of cancer and treatment of this disease with a primary focus on human cancer or mammalian models. Areas of interest include (but are not limited to) the genetics and epigenetics of cancer in humans or mouse models, tumor-host interactions, tumor metastasis, tumor immunology, cancer genomics, and the use of mouse models to dissect mechanisms of tumor initiation and progression. The successful candidate will have the opportunity to provide leadership in the field of cancer biology at the university in the future. This position is open at any level (tenure-track or tenured). *Applications should be submitted online through https://aprecruit.berkeley.edu/apply/JPF00217. See above application details.*

Emerging & Neglected Diseases
We seek candidates at the Full or Associate Professor level focused in all areas of infectious diseases, especially in human emerging and neglected infectious agents of global health importance. The successful candidate should also be interested in serving as a member of the faculty leadership group for the Wheeler Center for Emerging & Neglected Diseases (CEND) to manage existing programs and develop new initiatives and programs that further the mission of CEND, and to collaborate with the dynamic group of CEND-affiliated faculty from diverse schools and departments on campus. High priority will be given to candidates with international research collaborations, a translational global health research focus, and/or innovative approaches for understanding emerging and neglected infectious diseases. Candidates should be currently in a tenure level or equivalent position, or approaching a tenure decision at their current institution. *Applications should be submitted online through https://aprecruit.berkeley.edu/apply/JPF00216. See above application details.*

Memorial Sloan-Kettering Cancer Center
The Best Cancer Care. Anywhere.

FACULTY POSITIONS

Center for Stem Cell Biology & Developmental Biology Program
Sloan-Kettering Institute

The Center for Stem Cell Biology (CSCB) and the Developmental Biology Program are seeking innovative individuals who have strong records of research accomplishments in stem cell biology for tenure-track positions at the Assistant Member level (equivalent to Assistant Professor). The CSCB was established to further the interaction of researchers with active stem cell research programs at the Center, to enhance and build novel stem cell related resources and to recruit leading-edge stem cell faculty. The CSCB is interested in research in any aspect of stem cell biology, including the study of stem cells in model organisms, tissue stem cells and the biology and applications of human embryonic stem cells or induced pluripotent stem cells. Candidates with a strong interest in applying developmental approaches to studying stem cell biology are particularly encouraged to apply.

Applicants should have a PhD and/or MD degree, productive postdoctoral experience, dedication to important problems in stem cell biology, and the potential to develop a strong independent program in stem cell research. The successful candidate will be appointed in the Developmental Biology Program and will become a member of the CSCB. Successful candidates are also eligible to hold additional appointments at the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Cornell Graduate School of Medical Sciences, as well as the Tri-Institutional MD/PhD Training Program.

The successful applicant will have access to outstanding resources including expanded state-of- the-art facilities for human pluripotent stem cells, high-throughput chemical and genetic screening, mouse genetics, genomics, flow cytometry, advanced imaging and cancer biology. Memorial Sloan-Kettering offers a unique and exciting multidisciplinary research environment. Faculty in the CSCB participate in the Tri-institutional stem cell initiative (with Weill Cornell and Rockefeller University) that links stem cell researchers across neighboring institutions.

The deadline for applications is **November 1, 2013**. Interested candidates should visit **http://facultysearch.ski.edu** to access the on-line faculty application. Please visit the site as soon as possible, as it contains important information on the required application materials, including deadlines for submission of letters of reference.

Inquiries may be sent to **Tiffany Lennon at lennont@mskcc.org, Dr. Lorenz Studer, Director of the CSCB, at studerl@mskcc.org, or Dr. Kathryn Anderson, Chair of the Developmental Biology Program, at k-anderson@ski.mskcc.org**.

facultysearch.ski.edu

MSKCC is an equal opportunity and affirmative action employer committed to diversity and inclusion in all aspects of recruiting and employment. All qualified individuals are encouraged to apply and will receive consideration without regard to race, color, gender, gender identity or expression, sexual orientation, national origin, age, religion, creed, disability, veteran status or any other factor which cannot lawfully be used as a basis for an employment decision.

University of Wisconsin-Madison

The Department of Nutritional Sciences invites applications for a tenure-track faculty position at the **Assistant Professor** level. The successful candidate will be expected to develop a nationally competitive research program relevant to the multidisciplinary field of nutrition and health. Although all research areas will be considered and are encouraged, targeted themes include the role of the intestinal microbiome in obesity, diabetes, and other metabolic disorders, as well as the interaction between nutrients and epigenetic regulation. Research may incorporate molecular, biochemical, physiological, metabolic, genomic and/or clinical approaches. In addition to obesity and energy metabolism, current Department strengths include molecular mineral metabolism, gastrointestinal biology, developmental nutrition, genetic modifiers of metabolism, vitamin A/carotenoids, and community nutrition. The applicant will participate in graduate and undergraduate teaching, and will contribute to university service. Competitive start-up funding will be provided. Madison is renowned for a high quality of living and attractive cultural and outdoor activities. For full consideration, all application materials must be received by **November 30, 2013**. Please submit application materials including cover letter, curriculum vitae, description of accomplishments and future research goals (3 page limit), electronic reprints of up to three recent articles, and arrange to have three letters of reference provided. All materials should be submitted electronically to Professor Guy E. Groblewski, Search Committee Chair **PVL76888@nutrisci.wisc.edu**.

UW-Madison is an Equal Opportunity/ Affirmative Action Employer.

FACULTY POSITIONS AT THE ROCKEFELLER UNIVERSITY

The Rockefeller University seeks exceptional, interactive, and creative scientists to join its faculty. We invite applications from outstanding candidates for tenure-track positions.

The University has a laboratory-based organizational structure that fosters interdisciplinary research. We encourage applications in the following areas:

- **Chemical & Structural Biology**
- **Genetics & Genomics**
- **Immunology, Virology & Microbiology**
- **Medical Sciences, Systems Physiology & Human Genetics**
- **Molecular Cell Biology**
- **Neurosciences & Behavior**
- **Organismal Biology, Evolution, Ethology & Ecology**
- **Physical, Mathematical & Computational Biology**
- **Stem Cells, Development, Regeneration & Aging**

Details about specific subjects of research can be found at **http://www.rockefeller.edu/facultysearch.**

The Rockefeller University provides strong support for the research work of its faculty. The positions offer competitive salary, benefits and start-up funds, renovated laboratory space, access to state-of-the art core facilities and extensive opportunities for collaboration both within the University and with neighboring institutions.

Applications are being accepted electronically through our **Online Application System** at **http://oas.rockefeller.edu**. Applicants should follow the online application procedure.

The deadline for application submission is October 11, 2013.

If you have questions regarding submitting an application, please contact our Administrator at **facultysearch@rockefeller.edu**.

The Rockefeller University is an Affirmative Action/Equal Opportunity/VEVRAA Employer and solicits applications from women and under-represented minorities.

Memorial Sloan-Kettering Cancer Center
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FACULTY POSITION

Structural Biology Program
Sloan-Kettering Institute

The Structural Biology Program of the Sloan-Kettering Institute (www.ski.edu) invites applications for a tenure-track faculty position at the Assistant Member level (equivalent to Assistant Professor). We are interested in individuals who have an outstanding record of research accomplishments. Areas of interest include X-ray crystallography, NMR spectroscopy, single-molecule imaging, as well as the interface of structural, chemical and computational biology. Faculty will be eligible to hold graduate school appointments in the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Cornell Graduate School of Medical Sciences, as well as the Tri-Institutional MD/PhD Training Program.

The deadline for applications is **November 1, 2013**. Interested candidates should visit **http://facultysearch.ski.edu** to access the on-line faculty application. Please visit the site as soon as possible, as it contains important information on the required application materials, including deadlines for submission of letters of reference.

Informal inquiries may be sent to **Julie Kwan at kwanj@mskcc.org or Dr. Nikola Pavletich, Chair, Structural Biology Program at pavletin@mskcc.org.**

facultysearch.ski.edu

MSKCC is an equal opportunity and affirmative action employer committed to diversity and inclusion in all aspects of recruiting and employment. All qualified individuals are encouraged to apply and will receive consideration without regard to race, color, gender, gender identity or expression, sexual orientation, national origin, age, religion, creed, disability, veteran status or any other factor which cannot lawfully be used as a basis for an employment decision.

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Faculty Positions in Theoretical Physics

at Ecole polytechnique fédérale de Lausanne (EPFL)

The School of Basic Sciences at EPFL anticipates making two faculty appointments at the level of tenure track Assistant Professor in its Institute of Theoretical Physics (ITP). In exceptional cases, appointments at a higher level could be considered.

Successful applicants are expected to establish an internationally recognized research program. The relevant fields of research include condensed matter physics, strongly correlated systems and statistical/biological physics. Candidates with analytical and/or computational expertise will be considered. The appointed professors will be strongly committed to excellence in teaching physics at both the undergraduate and graduate levels.

EPFL offers internationally competitive salaries, benefits, and start-up resources for scientific equipment as well as annual resources for PhD students, scientific staff and consumables.

Applications including curriculum vitae, publication list, statement of research plans and teaching interests as well as the names and addresses (including email) of at least five references should be submitted in PDF format via the website http://sbpositions.epfl.ch/applications/ by **October 31, 2013**

For additional information, please contact **Professor Alfredo Pasquarello** (alfredo.pasquarello@epfl.ch) or consult the following websites: http://www.epfl.ch, http://sb.epfl.ch and http://itp.epfl.ch

The EPFL School of Basic Sciences aims for a strong presence of women amongst its faculty, and qualified female candidates are strongly encouraged to apply.

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Faculty Position in Physics of Biological Systems

at Ecole polytechnique fédérale de Lausanne (EPFL)

The School of Basic Sciences at EPFL seeks to appoint a tenure track Assistant Professor of experimental biophysics in its Institute of Physics of Biological Systems. In exceptional cases, appointments at a higher level could be considered.

The successful applicant is expected to establish a creative, internationally recognized research program within the broad domain of the biophysics of structure, dynamics and function from the molecular to organismal levels. The open position is offered in an environment of both theoretical and experimental research at the interface between physical and biological sciences. Existing research facilities are particularly strong in bio-imaging and electron microscopy and include access to the Swiss light source at PSI for synchrotron radiation. The appointed Professors will enjoy close contacts within physics, with the other EPFL Schools (i.e., Life Sciences and Engineering) as well as with the nearby universities and university hospitals. The appointed professor will be strongly committed to excellence in teaching physics at both the undergraduate and graduate levels.

We offer internationally competitive salaries, benefits, and start-up resources for scientific equipment as well as annual resources for PhD students, scientific staff and consumables.

Applications including curriculum vitae, publication list, statement of research plans and teaching interests as well as the names and addresses (including email) of at least five references should be submitted in PDF format via the website http://sbpositions.epfl.ch/applications/ by **October 31, 2013.**

For additional information, please contact **Professor Giovanni Dietler** (giovanni.dietler@epfl.ch) or consult the following websites: http://www.epfl.ch, http://sb.epfl.ch, http://ipsb.epfl.ch and http://sv.epfl.ch

The EPFL School of Basic Sciences aims for a strong presence of women amongst its faculty, and qualified female candidates are strongly encouraged to apply.

Junior Faculty Position, Vollum Institute
Oregon Health & Science University, Portland OR

The Vollum Institute (**www.ohsu.edu/vollum**) solicits applications from exceptional, creative and interactive neuroscientists for a junior faculty position, and also invites applications from candidates at an early stage in their career. **We particularly encourage applications from candidates whose research programs combine electrophysiology with imaging, molecular or optogenetic approaches to understand the brain at the cellular, circuit or systems level.**

The Vollum Institute offers competitive salary, benefits and start-up funds and ample access to numerous state-of-the-art core facilities that include cutting-edge light and electron microscopes, and extensive opportunities for collaboration, both within the Institute and throughout the University.

Vollum appointments are full-time research positions with minimal teaching requirements. The Vollum is allied with the Neuroscience Graduate Program, providing opportunities for teaching and access to a pool of exceptional students.

OHSU is an equal opportunity/affirmative action employer committed to maintaining diversity in its faculty. Candidates can apply by sending an electronic copy of their curriculum vitae, a description of research plans and goals, and three reference letters to the Vollum Faculty Search Committee (**volljob@ohsu.edu**) by **December 1, 2013**.

OREGON HEALTH & SCIENCE UNIVERSITY

BIOCHEMISTRY AND CELL BIOLOGY FACULTY SEARCH
Rice University Biochemistry and Cell Biology
http://www.rice.edu/

RICE

Applications are invited for two open-rank faculty positions in broad areas of biological research including biochemistry; cell and developmental biology; and systems, synthetic and physical biology. Applicants using experimental and/or theoretical biological approaches that are interdisciplinary with chemistry, physics, engineering, or computational methods are especially encouraged to apply. Candidates must have a Ph.D., postdoctoral training, and outstanding potential in research and teaching. Successful candidates are expected to develop and maintain a vibrant research program supported by extramural funding and participate in the education and mentorship of graduate and undergraduate students.

Review of applications will commence **October 15, 2013** and continue until the positions are filled. Please compile a PDF containing a cover letter, curriculum vitae, summary of past research accomplishments and future research plans, summary of teaching goals and email to **BCBSearch@rice.edu**. Arrange for four letters of reference to be sent to the same email address.

Rice University is an Equal Opportunity/ Affirmative Action Employer; women and minority candidates are especially encouraged to apply.

Harry S. Truman Fellowship
in National Security Science and Engineering

Sandia National Laboratories

Sandia National Laboratories is one of the country's largest research facilities employing nearly 8,500 people at major facilities in Albuquerque, New Mexico and Livermore, California. Please visit our website at ***www.sandia.gov***.

We are searching for outstanding Ph.D. candidates for the **President Harry S. Truman Fellowship in National Security Science and Engineering**. Candidates are expected to have solved a major scientific or engineering problem in their thesis work, or will have provided a new approach or insight to a major problem, as evidenced by a recognized impact in their field.

Sandia's research focus areas are: bioscience, computing and information science, engineering science, materials science, nanodevices and microsystems, radiation effects science, high energy density physics, and geoscience.

Candidates must have received a Ph.D. within the past 3 years, or will complete all Ph.D. requirements by commencement of appointment. Candidates must be seeking their first national laboratory appointment (pre postdoc internships excluded), have excellent academic (minimum 3.5 undergraduate and 3.7 graduate GPA preferred) and research qualifications, good communication skills, and enjoy working in a team-oriented, dynamic environment.

This initial one-year appointment may be extended, at management's discretion, for two additional one-year appointments. The salary is $111,200 per year plus benefits and additional funding for the chosen research proposal. This position requires the ability to obtain and maintain a United States Department of Energy Security Clearance.

For complete application instructions, please visit: http://www.sandia.gov/careers/students_postdocs/fellowships/truman_fellowship.html

Please submit the complete package to: Yolanda Moreno, Sandia National Laboratories, P.O. Box 5800, MS0359, Albuquerque, New Mexico 87185-0359, or email: ymoreno@sandia.gov. Please reference: **Job ID: 643454. All materials and online application must be received by November 1, 2013.**

U.S. Citizenship Required.
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TENURE TRACK FACULTY POSITION
Cell Biology Program
Sloan-Kettering Institute

The Cell Biology Program at Sloan-Kettering Institute (www.ski.edu) has initiated a search for a tenure-track faculty member. We are interested in outstanding individuals who have the potential to develop an innovative, independent research program that complements and enhances our existing strengths.

Candidates with research interests in exciting areas of eukaryotic cell biology and using a variety of experimental approaches and systems are encouraged to apply. New faculty will be eligible to hold graduate school appointments in the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Cornell Graduate School of Medical Sciences of Cornell University, as well as the Tri-Institutional MD/PhD Training Program. Sloan-Kettering has an outstanding infrastructure as well as state-of-the-art core facilities, and we are expanding our research programs.

The deadline for applications is **November 1, 2013**. Interested candidates should visit **http://facultysearch.ski.edu** to access the on-line faculty application. Please visit the site as soon as possible, as it contains important information regarding the required application materials, including deadlines for submission of letters of reference. Informal inquiries may be sent to **Marie Aiello** at **aiellom@mskcc.org** or **Dr. Alan Hall, Chair, Cell Biology Program** at **halla@mskcc.org**.

facultysearch.ski.edu

MSKCC is an equal opportunity and affirmative action employer committed to diversity and inclusion in all aspects of recruiting and employment. All qualified individuals are encouraged to apply and will receive consideration without regard to race, color, gender, gender identity or expression, sexual orientation, national origin, age, religion, creed, disability, veteran status or any other factor which cannot lawfully be used as a basis for an employment decision.

FACULTY POSITIONS
Physiology & Pharmacology



The Department of Physiology & Pharmacology at Des Moines University invites applicants for open-rank, tenure-track faculty positions. Qualifications include preparation and expertise in one or more of the following areas:

Cardiovascular Physiology; Respiratory Physiology; Endocrine Physiology or Medical Pharmacology

We are committed to advancing our research enterprise and fostering an environment conducive to scholarly success through the cultivation of distinctive faculty and student researchers who discover and disseminate new knowledge. The expectation is for faculty to participate in scholarly activity including grant application, publications, research, as well as teaching to graduate and medical school students. Candidates should demonstrate the potential to develop an innovative and extramurally funded research program and have a Ph.D. or equivalent plus a minimum of two years postdoctoral experience. Compensation and lab start-up costs are funded by the University and are not dependent on grant funding.

Please submit a letter of application, a CV, a concise statement of teaching interests and educational philosophy, a well-defined research plan including specific aims and objectives and three references using the online applicant tracking system at ***www.dmu.edu/employment***. Candidates with questions specific to this position may contact Department Chair Dr. Matt Henry at 515-271-1434.

For more information on all that the Des Moines area has to offer regarding housing, schools, entertainment, lower cost of living and more, visit ***www.desmoinesmetro.com***.

DES MOINES UNIVERSITY

Job description, faculty benefit summary and information on Des Moines University are available at www.dmu.edu/employment.

Review of applications will begin immediately and continue until the positions are filled.

Des Moines University is an equal opportunity/affirmative action employer. The University seeks excellence through diversity among its administrators, faculty, employees and students. The University prohibits discrimination on the basis of race, color, national origin, creed, religion, age, disability, sex, gender identity, sexual orientation, veteran status, genetic information or any other legally protected status. Applications by members of all underrepresented groups are encouraged.

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

Faculty Position in Microbiota of the Gut
at Ecole polytechnique fédérale de Lausanne (EPFL)

The School of Life Sciences at EPFL is expanding its Global Health Institute and invites applications for a faculty position in Microbiology and Infectious Diseases. We are primarily seeking candidates for a **tenure track assistant professor position** but in exceptional cases more experienced candidates will be considered.

Successful candidates will develop an independent and vigorous research program, participate in both undergraduate and graduate teaching, and supervise PhD students and postdoctoral fellows.

Preference will be given to applicants investigating the impact of the **microbiota on human health, metabolism, physiology and immune responses.**

Significant start-up resources, research budget and state-of-the-art research infrastructure are available, within the framework of a campus that fosters very strong interactions between life sciences, basic science, informatics and engineering. Translational research is encouraged. Salaries and benefits are internationally competitive.

Candidates should upload their application as PDF files at the address http://globalhealth-recr.epfl.ch, and should include a curriculum vitae, publication list, brief statement of research and teaching interests, names and e-mail addresses of 3 references. Screening will start on **December 1st, 2013** with interviews in the spring.

Further questions can be addressed to:

Professor Stewart Cole
Director of the Global Health Institute
EPFL – SV – GHI
Station 19
CH-1015 Lausanne
Switzerland

Email: GHI-recruit@epfl.ch

For additional information on EPFL, please consult the web sites www.epfl.ch, sv.epfl.ch

EPFL is committed to balancing gender within its faculty and strongly encourages suitably qualified female candidates to apply.

STANFORD UNIVERSITY
Stanford Institute for Chemical Biology

The Stanford Institute for Chemical Biology is an independent institute at Stanford University, formed in partnership with the Schools of Medicine, Humanities and Sciences, and Engineering. The Institute is seeking applicants for a tenure-track faculty position at the junior level (Assistant or untenured Associate Professor). Candidates are expected to have earned a Ph.D. or M.D. degree in any discipline of science, engineering or medicine. We will consider candidates knowledgeable in the general area of chemical biology. All areas encompassed by the field of chemical biology are acceptable. In general, we give higher priority to the overall originality and promise of the candidate's work than to the sub-area of specialization.

The successful candidate will have his/her primary appointment in a department within the School of Medicine, Humanities and Sciences, or Engineering. He/she will be expected to teach and/or perform clinical service within this department in a manner that is consistent with standard practices for tenure-track faculty within that department. The candidate will also be expected to develop a world-class research program in chemical biology. Candidates should be seeking a stimulating interdisciplinary environment in which to pursue teaching and research. We anticipate that the faculty member will develop interactions with faculty not only in his/her home department but also in other departments and Schools at Stanford and at the Stanford Synchrotron Radiation Laboratory.

Applications should be addressed to Professor James K. Chen, Search Committee Chair and include a curriculum vitae, a description of future research plans, and a teaching statement. These materials should be submitted electronically as a single PDF to **sicbsearch@stanford.edu** by **November 1, 2013** to ensure full consideration. Applicants should also have three reference letters submitted to **sicbsearch@stanford.edu** by the application deadline.

Stanford University is an Equal Opportunity Employer and is committed to increasing the diversity of its faculty. It welcomes nominations of and applications from women and minority groups, as well as others who would bring additional dimensions to the university's research, teaching, and clinical missions.

PRINCETON UNIVERSITY
Assistant Professor Positions Available

The Lewis-Sigler Institute for Integrative Genomics at Princeton University invites applications for tenure-track faculty positions at the Assistant Professor level; in exceptional cases, more senior appointments may be considered. We are seeking outstanding scientists with strong interest and experience in quantitative, systems-level approaches to understanding any area in modern experimental molecular biology, chemistry, or evolutionary biology. Appointments at the Lewis-Sigler Institute are made jointly with an appropriate home department. A strong record of experimental work and quantitative analysis is essential. The successful candidate will have research laboratories at the Institute, and teaching responsibilities (both graduate and undergraduate) will be shared between the Institute and the home department.

The Lewis-Sigler Institute for Integrative Genomics, housed in the Carl Icahn Laboratory at Princeton University, was established to innovate in research and teaching at the interface of modern biology and the more quantitative sciences. The Institute provides significant support to its faculty through heavy investment in state-of-the-art research infrastructure, an NIH-funded graduate training program, and a high level of administrative support as well.

Essential Qualifications: All applicants must have a Ph.D., M.D., or equivalent degree. In addition, applicants must have a very strong record of research productivity, demonstrate the ability to develop a rigorous research program, and be committed to teaching at both the undergraduate and graduate levels.

How to Apply: Applications must be submitted online at: **http://jobs.princeton.edu/applicants/Central?quickFind=64204**, requisition **#1300612** and should include a cover letter, curriculum vitae, a two-page research description, as well as contact information for three references. Applications will be reviewed beginning on **October 15, 2013**.

Princeton University is an Equal Opportunity Employer and complies with applicable EEO and affirmative action regulations.



The Leipzig School of Human Origins
- An International Max Planck Research School -

by

The University of Leipzig

and

The Max Planck Institute for Evolutionary Anthropology

The **Leipzig School of Human Origins** offers a unique interdisciplinary graduate program to study the evolutionary history of humans and great apes. Graduate students are accepted into one of the following areas, but are encouraged to take part in courses and seminars from all three disciplines:

Comparative and Molecular Primatology

Evolutionary and Functional Genomics, Ancient DNA, Molecular Anthropology and Genome Bioinformatics

Human Paleontology, Prehistoric Archaeology and Archaeological Science

The language of the school is English. Visit www.leipzig.de for information on living in Leipzig, Germany, in the center of Europe.

For project and application details go to **www.leipzig-school.eva.mpg.de** or contact us at:

e-mail: leipzig-school@eva.mpg.de
phone: ++49 (0) 341 3550-0
fax ++49 (0) 341 3550-119

Application deadline: December 01, 2013

FACULTY POSITION IN SYNTHETIC ORGANIC CHEMISTRY
Department of Chemistry
BIOMEDICAL CHEMISTRY INSTITUTE
Arts and Science

The Department of Chemistry at New York University (NYU), located in Greenwich Village in the heart of Manhattan, invites applications for a faculty position in synthetic organic chemistry as part of its Biomedical Chemistry Institute. While we expect to hire at the junior level, exceptional senior level candidates will be considered. The anticipated start date is September 1, 2014, pending budgetary and administrative approval. The Department of Chemistry at NYU is implementing a significant growth plan, including the creation of the Biomedical Chemistry Institute and the Molecular Design Institute, and the recent hire of five senior and five junior faculty members. Duties will include undergraduate and graduate teaching. Applicants should have an outstanding record of research and a commitment to teaching.

Applications must include a curriculum vitae, a list of publications, and statements of future research and teaching plans. These materials, as well as three reference letters, must be submitted to our web-based application system using the following link: **http://chemistry.fas.nyu.edu/object/chem.nyufacultypositions**. *Application review will begin* ***October 15, 2013***. If you have any questions about this position, please send an email to **chemistry.search@nyu.edu**.

NEW YORK UNIVERSITY

NYU is an Equal Opportunity/Affirmative Action Employer.

WWW.NIH.GOV
Positions @ NIH
THE NATIONAL INSTITUTES OF HEALTH

The NIH Intramural Research Program is Recruiting Tenure-Track "Earl Stadtman Investigators"

The National Institutes of Health, the U.S. government's premier biomedical and behavioral research enterprise, is pleased to announce its fifth annual call for "NIH Earl Stadtman Investigators," a broad recruitment of tenure-track investigators for all NIH intramural programs. Scientific discoveries from our intramural laboratories, with their extensive infrastructure and critical mass of expertise, have a crucial role in both maintaining America's research excellence and advancing medical treatments and cures.

Come join the team whose hallmarks are stable funding, intellectual freedom, shared resources, and access to a wide range of scientific expertise. We seek creative, independent thinkers eager to take on high-risk, high-impact research. A fantastic array of early-career scientists already have been hired through the "Stadtman" recruitment in the last four years.

A variety of basic and translational/clinical positions are available, with areas of active recruitment including (but not limited to): Biochemistry, Biomedical Engineering, Biophysics, Biostatistics, Cancer Biology, Cell Biology, Cell Metabolism, Chemical Biology, Chromosome Biology, Circadian Biology, Computational Biology, Developmental Biology, Epidemiology, Genetics, Genomics, Health Disparities, Hearing & Balance, Immunology, Infectious Diseases, Microbiology, Molecular Pharmacology, Neurodevelopment, Neurosciences, Sensory Biology, Structural Biology, Systems Biology, Toxicology, Translational Research, and Virology.

Who we are: Among our approximately 1,100 principal investigators and 5,000 trainees are world-renowned experts in basic, translational, and clinical research. Our strength is our diversity in pursuit of a common goal, to alleviate human suffering from disease. Similar to academia, we offer our scientists the opportunity to mentor outstanding trainees at all levels (e.g., graduate students and postdoctoral fellows) in a research setting.

Whom we seek: For this broad, trans-NIH recruitment effort, we seek talented, early-career scientists with a clear and creative research vision who wish to contribute to the nation's health.

Qualifications/eligibility: Candidates must have an M.D., Ph.D., D.D.S./D.M.D., D.V.M, D.O., R.N./Ph.D., or equivalent doctoral degree and have an outstanding record of research accomplishments as evidenced by publications in major peer-reviewed journals. Applicants may be in early stages of their research careers or non-tenured early-to-mid career scientists. Appointees may be U.S. citizens, resident aliens, or non-resident aliens with, or eligible to obtain, a valid employment-authorization visa.

How to apply: Applicants must submit four items: (1) a CV; (2) a three-page proposal titled Research Goals, i.e., the research you hope to perform at the NIH; (3) a one-page statement titled Long-term Research Vision and Impact, i.e., what you hope to achieve for yourself, your field, and society; and (4) contact information for three professional references. Submit these through our online application system at http://tenuretrack.nih.gov/apply between August 1 and 11:59 p.m. EDT October 1, 2013. You will be asked to designate a primary and secondary scientific area of expertise to aid in assigning your application to the appropriate review committee. Requests for letters of recommendation will be sent to your references when you submit your application. Reference letters will be accepted via upload to the website until 11:59 p.m. EDT October 15, 2013. We cannot accept paper applications.

What to expect: Search committees of subject-matter experts will review and evaluate applicants based on publication record, scientific vision and potential scientific impact of current and proposed research, demonstrated independence, awards, and references. The committees will identify the most highly qualified candidates to invite to the NIH for a lecture in November or December 2013, open to the NIH scientific staff, and for subsequent interviews with the search committees. Search committee chairs and NIH Scientific Directors, who lead our intramural programs, will identify finalists for possible recruitment as Earl Stadtman Investigators. Candidates not selected as finalists can be considered for other open NIH research positions. The entire process from application review to job offer may take several months, depending on the volume of applications.

We call upon individuals who will open our eyes to possibilities we haven't yet envisioned, to complement our scientific mission and enhance our research efforts. More information about our program is at http://irp.nih.gov. The inspiring story of Earl and Thressa Stadtman's research at the NIH is at http://history.nih.gov/exhibits/stadtman. Specific questions regarding this recruitment effort may be directed to Dr. Roland Owens, Assistant Director, NIH Office of Intramural Research, at owensrol@mail.nih.gov. DHHS and NIH are Equal Opportunity Employers.



2013 Annual Top Employers Survey

Special Career Feature: October 25, 2013

Reserve your ad by October 8 to guarantee space.*

*Ads accepted until October 21 if space is still available.

Who is No. 1 this year?

Science publishes its 12th annual Top Employers Survey on October 25, 2013. *Science* has a long history of providing a forum for scientists to express their opinions about the biotech and pharma industry. For 2013, we gathered the responses from 3,600 scientists who had plenty to say about the industry.

Advertise in this issue to reach both ACTIVE and PASSIVE job seekers. Here's how:

1. Scientists in the biotech/pharma community eagerly anticipate the results of this survey every year. By announcing your openings in this special feature, your reach goes beyond active job seekers to those involved in the field, targeting elusive passive job seekers at the same time.
2. Your association with this issue tells prospective recruits that you are among the best. You have a unique opportunity to brand your company as a leader. Reach the scientists that your competitors are reaching and promote your advantages.

Start building your pipeline today with *Science*.

Over
84,000
Science* print readers work in industry—reach these passive job seekers!*

To book your ad:

E-mail: advertise@sciencecareers.org

Or telephone us:

US/Canada/South America: 202-326-6582

Europe/India/Australia/New Zealand/ Rest of World: +44 (0) 1223 326500

Japan: +81-(0)90-9110-1719

China/Korea/Singapore/Taiwan/ Thailand: +86-1367-1015-294

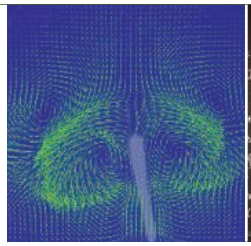
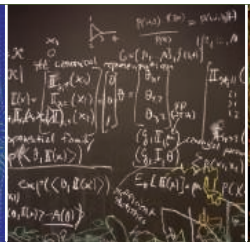
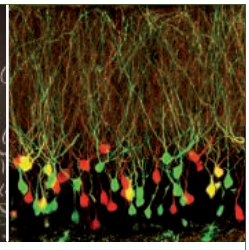
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ScienceCareers.org

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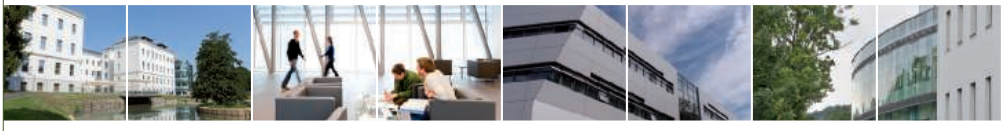
CALL FOR
Professors and Assistant Professors

IST Austria invites applications for **tenured** and **tenure-track leaders** of **independent research groups** in following fields: **Physics** | **Chemistry** | **Biology** | **Neuroscience** | **Earth Science** | **Mathematics** | **Computer Science** | **Interdisciplinary Areas**

The Institute is dedicated to basic research and graduate education in the natural and formal sciences. The successful candidates will receive a substantial annual research budget, are expected to apply for external research grants and to participate in the Graduate School.

Deadline for receiving Assistant Professor applications: November 15, 2013
Open call for Professor applications
Further information and online application: **www.ist.ac.at/professor-applications**

IST Austria values diversity and is committed to equality. Female researchers are encouraged to apply.



IST AUSTRIA
Institute of Science and Technology

北京航空航天大學
BEIHANG UNIVERSITY

Faculty Positions Available in Beihang University, China

Established in 1952, located in Haidian District, Beijing, Beihang University is one of the top research-oriented universities in China, focusing on fundamental cutting edge research and high-level education, covering such diverse fields as science, engineering, technology, humanities, economics, management and law. One of the first universities funded by China's "211" and "985" programs, it has seven national key laboratories and twenty-five provincial and ministerial key laboratories. At present, the university has a total area of two million square meters, and over 3800 faculty and staff.

Beihang University is on a clear path to become a world-class university in many engineering and science disciplines. As part of Beihang's further pursuit for excellence in research and education, we have expanded our global search for the best research talent to join our International Research Institute for Multidisciplinary Science (IRIMS). Five independent international research centers (IRC) were established recently under the name of IRIMS. As the core part of IRIMS, IRCs are devoted to establish a world-class, advanced and multidisciplinary research platform.

Beihang University invites applications for full-time Professors, Associate Professors and excellent scientists. Preference will be given to candidates whose research emphasis demonstrates the potential to complement and advance the IRIMS existing research strengths. Successful candidates will be provided competitive salaries and start-up funds.

Positions Available

- Position offered by the Recruitment Program of Global Experts (1000 Plan Professorship)
- Position offered by the Chang Jiang Scholars Program
- Position offered by the Recruitment Program of Global Young Experts (1000 Plan Professorship for Young Talents)
- Position offered by Beihang University's Zhuoyue Program of Professors
- Position offered by Beihang University's Zhuoyue Program of Associate Professors.

Interested individuals should send curriculum vitae by email to **rscrcb@buaa.edu.cn**, with "Faculty Application from *Science*" in the title. For more information, please visit the university's Human Resource Department website **http://rsc.buaa.edu.cn/**, or contact us by email **rscrcb@buaa.edu.cn** or by telephone **86-010-82317779**.

UMASS AMHERST

Two Tenure-Track Assistant Professor Positions:

Neurobiology and Physiological Ecology

The Biology Department at the University of Massachusetts Amherst invites applications for two tenure-track Assistant Professor positions to start as soon as September 1, 2014. One position is in the area of Neurobiology and the other is in the area of Physiological Ecology. We seek individuals with outstanding research, a strong commitment to teaching, and the potential to develop and maintain an extramurally funded research program. The Biology Department provides an interactive and broad research environment, with faculty research spanning all levels of biological organization. Evaluation of applications for both positions will begin on October 1, 2013, and continue until the positions are filled.

1) **Neurobiology:** We encourage applications from neurobiologists who study neural development, neural structure and function, neurodegenerative diseases and/or aging at the molecular and cellular level, but applications from other areas will also be seriously considered. The successful candidate will contribute to the department's teaching mission through teaching in Neurobiology and will train students at the undergraduate and graduate levels. Application materials may be sent via email to: neurosearch@bio.umass.edu.

2) **Physiological Ecology:** We seek a biologist whose research spans the interface of physiology and ecology, investigating how physiological adaptations help organisms adapt to real world environmental challenges. We are especially interested in candidates whose research programs include laboratory and field components. The successful candidate will contribute to the department's teaching mission through teaching in the area of Physiology and will train students at the undergraduate and graduate levels. Application materials may be sent via email to: physecosearch@bio.umass.edu.

A Ph.D. in Biology or a related field and postdoctoral experience are required. Application materials should include a curriculum vitae, research plan, and teaching statement. The applicant should also have three reference letters sent to the appropriate address above. If needed, paper applications can be sent to: Neurobiology Search #R46720, or Physiological Ecology Search #R46721, Biology Department, Attn: Zoe Crowley, 611 North Pleasant Street, University of Massachusetts, Amherst, MA 01003.

The University of Massachusetts Amherst is an Affirmative Action/Equal Opportunity Employer. Women and members of minority groups are encouraged to apply. In reviewing applicants, we will favorably factor personal experiences, or experiences helping others, in overcoming barriers to an academic career or degree and/or other experiences with students and colleagues from diverse backgrounds or perspectives.

Regulatory Systems Biology Faculty Position

The California Institute of Technology invites applications for a tenure-track assistant professor position in the Division of Biology and Biological Engineering. We are interested in candidates who will approach gene-centered questions in the fundamental biology of multicellular organisms from a complex system perspective. Relevant research areas include but are not limited to gene network and circuit design problems in developmental biology, evolution of gene regulatory networks, and design principles in gene regulatory circuits.

Candidates with strong commitments to research and teaching excellence are encouraged to apply. Initial appointments at the assistant professor level are for four years, and they are contingent upon completion of the Ph.D. degree.

Please submit on-line application at: **http://biology.caltech.edu/Positions**, and include a brief cover letter; curriculum vitae; relevant publications, a description of proposed research; and a statement of teaching interests. Applicants should arrange to have four reference letters uploaded.

Application review will commence immediately and continue until **January 1, 2014**.

The California Institute of Technology is an Equal Opportunity/Affirmative Action Employer. Women, minorities, veterans, and disabled persons are encouraged to apply.

MIT Massachusetts Institute of Technology



Come work with us!

Assistant Professors
Neuroscience and Human Cognition

The Department of Brian & Cognitive Sciences (BCS) (http://bcs.mit.edu) and **The McGovern Institute for Brain Research at MIT** (http://mcgovern.mit.edu) are looking to hire up to three tenure-track faculty at the assistant professor level who will work in one or more of the following four areas: i) *Neuroscience* in nonhuman animals, especially if the candidate's work bridges levels using a variety of tools and/or has relevance for understanding the neural basis of brain disorders. ii) *Computational* approaches to intelligence, cognition or neuroscience; an experimental component to the candidate's research would be viewed as a positive but is not necessary. An affiliation with Electrical Engineering and Computer Science, the Computer Science and Artificial Intelligence Laboratory (CSAIL), or other allied departments is possible. iii) *Human cognitive neuroscience*, including MRI, MEG, and neurophysiological approaches. iv) *Human cognition* using behavioral methods, especially in the areas of language and/or cognitive development.

Successful applicants are expected to develop and lead independent, internationally competitive research programs and to share in our commitment to excellence in undergraduate and graduate education by teaching courses and mentoring graduate and undergraduate research. PhD must be completed by start day of employment and some postdoctoral training is preferred.

Please submit application materials – cover letter, CV, statement of research and teaching interests and representative reprints – online at https://academicjobsonline.org/ajo/jobs/3081. Please state research area in cover letter. To help direct the application, applicants should indicate which of the four areas listed above is their main research area by answering the mandatory questions included in the application. In addition, please arrange to have three letters of recommendation submitted online. Review of applications will begin on **November 15, 2013.**

MIT is an affirmative action employer, and we encourage applications from women and underrepresented minorities.

http://web.mit.edu

Faculty Positions in Basic and Clinical Neuroscience Research
SUNY Upstate Medical University

SUNY Upstate Medical University seeks scientists studying mechanisms of neurobiological function, disease and dysfunction at cellular, molecular and systems levels. Multiple tenure-track positions are open at senior and junior faculty levels of the New York State Empire Innovator Program, which aims to recruit world-class faculty to the SUNY system. Areas of particular interest include, but are not limited to neurotraumatic, neurodegenerative and neurodevelopmental disorders.

Candidates utilizing stem cell biology, biomarker development, or cutting-edge optical approaches are especially encouraged to apply. Positions are open to individual applicants or to research teams. Significant current external research funding strongly preferred, and required for senior applicants. Successful candidates will hold joint appointments in a basic science and one of several clinical departments, and will be expected to maintain a vigorous and independently funded research program. SUNY Upstate offers a highly competitive hard-moneyed state-line salary, a generous start-up package and access to a unique, integrated clinical-basic science research environment.

Neuroscientists at Upstate benefit from a new research building featuring 100,000 sq.ft. laboratory space equipped with state of the art facilities (see **http://www.upstate.edu/neuroscience**). Applicants should submit a curriculum vitae, statement of research interests and three letters of reference by December 1, 2013 for full consideration, to: **EIP Faculty Search c/o Barbara Humphrey, SUNY Upstate Medical University, 750 East Adams Street, Syracuse, NY 13210,** email: **eisearch@upstate.edu**, or apply online at: **www.upstate.edu/hr/jobs**, listing **#036887**.

UPSTATE MEDICAL UNIVERSITY

At SUNY Upstate Medical University we strive to promote a professional environment that encourages varied perspectives from faculty members with diverse life experiences. A respect for diversity is one of our core values. We are committed to recruiting and supporting a rich community of outstanding faculty, staff and students. We actively seek applications from women and members of underrepresented groups to contribute to the diversity of our university community in support of our teaching, research and clinical missions.

JOHNS HOPKINS UNIVERSITY

Bloomberg Distinguished Professor of Molecular and Cellular Neuroscience

A Bloomberg Distinguished Professorship in Molecular and Cellular Neuroscience, with a focus on brain development and function, is available at the Johns Hopkins University. This position is one of 50 new Bloomberg Distinguished Professorships designated for outstanding scholars who carry out interdisciplinary research and teaching in areas identified for significant growth at the University. The current position is linked to growth in the University-wide Science of Learning Initiative. The position will include joint tenure in the School of Medicine and the Krieger School of Arts and Sciences, crossing the Departments of Neuroscience, Psychological Brain Science, and/or Biology. The holder of this Bloomberg Distinguished Professorship will participate in research and teaching in both the School of Medicine and the Krieger School of Arts and Sciences. Applicants should possess distinguished records of achievement in both research in molecular and cellular neuroscience and the teaching of undergraduate, graduate, and medical students compatible with appointment to tenure at the Johns Hopkins University. Investigators interested in the molecular and cellular basis of nervous system development, synaptic plasticity, circuitry and function are invited to apply. Please submit a PDF file containing curriculum vitae to the email address below. The deadline for application is **November 1st, 2013**.

The Johns Hopkins University is committed to enhancing the diversity of its faculty and encourages applications from women and minorities. Please submit a PDF file containing curriculum vitae to the email address below.

Richard L. Huganir
Michela Gallagher
Co-Chairs Search Committee
The Johns Hopkins University
School of Medicine
725 North Wolfe Street, Hunterian 1009A
Baltimore, Maryland 21205
HopkinsNeuroBDPSearch@jhmi.edu

An EEO/AA Employer.

Tenure-Track Assistant Professorship in Chemistry (Inorganic) Harvard University

Candidates are invited to apply for a tenure-track assistant professorship in inorganic chemistry, broadly defined to include catalysis, synthesis, mechanism, materials, and energy-related research. The appointment is expected to begin on July 1, 2014. The tenure-track professor will be responsible for teaching at the undergraduate and graduate levels. We are seeking candidates who have an outstanding research record and a strong commitment to undergraduate and graduate teaching. Doctorate required by expected start date.

Candidates should arrange to have three letters of recommendation sent independently and provide a curriculum vitae, statement of teaching philosophy, list of publications, and outline of their future research plans. All applications and supporting materials must be submitted via the ARIeS portal (**http://academicpositions.harvard.edu/postings/4913**) no later than **October 15, 2013**.

Harvard is an Equal Opportunity/Affirmative Action Employer. Applications from women and minorities are strongly encouraged.

RUTGERS THE STATE UNIVERSITY OF NEW JERSEY

Senior Faculty Position in Computational Genetics

The Department of Genetics in the School of Arts and Sciences at Rutgers, The State University of New Jersey seeks an outstanding senior scientist to complement the existing faculty in computational genetics, moving our program into exciting new areas and expanding our existing strengths. Tenured appointment will be made at the Associate or Full Professor level. Areas of interest include, but are not limited to, population or evolutionary genetics, bioinformatics, statistical genetics, computational genomics, and analysis of complex genetic diseases. The successful candidate will be a member of the newly founded Center for Genome Variation and Evolution within the Genetics Department. Senior hires with appropriate leadership experience would be considered for directorship of this Center. Appropriate candidates will also be appointed to the Human Genetics Institute of New Jersey. Core resources and generous startup funds will be provided. Research space, including wet lab if needed, will be provided in the newly constructed Life Sciences Building.

The Department of Genetics is home to over 30 faculty with diverse interests and numerous well-funded research programs, and is part of a vibrant life sciences and computational community. Our computational group collaborates with other Department of Genetics faculty and Rutgers scientists within the Division of Life Sciences, the Departments of Computer Science and Statistics, the Waksman Institute, the Center for Advanced Biotechnology and Medicine, the Robert Wood Johnson Medical School, the BioMaPS Institute for Quantitative Biology, and the Center for Discrete Mathematics and Theoretical Computer Science (DIMACS). The New Brunswick/Piscataway campus is located in suburban central New Jersey, close to New York City, Philadelphia, beaches, and countryside. For more information on the Department and Rutgers see: **http://genetics.rutgers.edu/faculty/faculty-recruitment**.

Candidates must have a Ph.D. and/or M.D., demonstrated record of significant research, the potential to make substantial contributions as an independent investigator, and have a commitment to teaching undergraduate and graduate students. Applicants should submit a CV, a detailed statement of research interests, a teaching statement, and full contact information for three individuals willing to provide letters of reference. Applications should be submitted electronically at **http://apply.interfolio.com/22156** and inquiries made to **Ms. Laura Bué, bue@dls.rutgers.edu**. Review of applications will begin **October 15, 2013** and continue until the position is filled.

Rutgers University is an Equal Opportunity/Affirmative Action Employer committed to diversity. Women, minorities, and members of under-represented groups are encouraged to apply.

THE OHIO STATE UNIVERSITY

The **Department of Microbiology in the College of Arts and Sciences** at The Ohio State University (http://microbiology.osu.edu) invites applications for a faculty position at the **Assistant, Associate** or **Full Professor** level in the area of Microbial Genomics. The successful candidate will complement an established and active research faculty with expertise in microbial biochemistry, genetics, physiology and the analysis of environmental microbiomes. The candidate will have opportunities for collaboration through interaction with investigators in the Center for RNA Biology (CRB), the Mathematical Biosciences Institute (MBI), the Department of Microbial Infection and Immunity (MMI, College of Medicine) and the Center for Microbial Interface Biology (CMIB). Genomics research is also an integral component of a newly established campus-wide Discovery Theme program with initiatives in Energy and Environment, Health and Wellness, and Food Security and Production,

Applicants will have a Ph.D. and/or M.D. and established expertise in the application of genomic techniques in the area of genome evolution, metabolic capacity and diversity, gene expression, microbial community analysis or the interaction of microbes with their host in health and disease. Candidates are expected to establish and maintain an extramurally funded research program and to actively support our commitment to excellence in teaching at the undergraduate and graduate levels. Associate and Full Professor candidates will have internationally recognized research programs with evidence of sustained funding.

Applicants should submit a cover letter, curriculum vitae, and a statement of research and teaching interests, and three letters of reference. Inquiries may be directed to **Dr. Charles J. Daniels** (**daniels.7@osu.edu**). Review of applications will begin on **November 1, 2013** and we encourage submission before that date. However, applications will continue to be accepted until the position is filled. Please apply online through Academic Jobs Online at: **http://academicjobsonline.org**.

To build a diverse workforce Ohio State encourages applications from individuals with disabilities, minorities, veterans, and women. EEO/AA Employer. Ohio State is an NSF Advance Institution.

Tenure Track Faculty Positions in Neuroscience

Washington University in St. Louis

Department of Anatomy & Neurobiology

The Department of Anatomy & Neurobiology at Washington University School of Medicine is undergoing a major expansion and invites applications for tenure track Assistant Professor positions. We are seeking in **two concurrent searches** talented investigators who will develop an innovative research program in any field within the following two broad areas of neuroscience: **(1) Cellular and Molecular Neurobiology** including cellular and signaling mechanisms regulating the assembly and function of neural circuits, synaptic plasticity, and developmental disorders of cognition; **(2) Systems Neuroscience** including studies of neural circuit functions in genetically tractable model organisms and higher cognitive functions in non-human primates.

Applicants should **email** a single PDF file that includes a cover letter, CV, summary of research accomplishments and plans, and also request 3 letters of support be **emailed** to **NeuroSearch@wustl.edu** or **SystemsSearch@wustl.edu** c/o Azad Bonni, MD, PhD, Chairman, Department of Anatomy & Neurobiology, Washington University School of Medicine, St Louis, MO 63110. Review of applications including letters of support will begin on **October 15, 2013**.

Washington University is an Equal Opportunity Employer AA/EOE M/F/D/V.

Plant Biologist

NM STATE UNIVERSITY

The Department of Biology at New Mexico State University invites applications for a 9-month, tenure-track Assistant Professor position in Plant Biology. Applicants must have a Ph.D. in Biology or a related field, a track record of research productivity commensurate with experience, a demonstrated commitment to undergraduate and graduate education and a minimum of one year of postdoctoral experience. The successful candidate will develop an externally funded research program in any area of plant biology (including physiology, ecology, cell/developmental biology and microbe interactions) and teach courses in plant biology and related areas at the undergraduate and graduate level.

Applicants should submit a single pdf consisting of a cover letter, CV, and concise (2-pages each, maximum) statements of (a) research interests and accomplishments and (b) teaching philosophy and experience, by email to ***biologysearch@nmsu.edu***. Applicants should arrange to have three letters of reference sent by e-mail to the same address. Preference will be given to completed applications submitted by the initial review date of October 18, 2013. Applications lacking required components may not be reviewed.

The Department of Biology offers undergraduate majors in Biology, Microbiology, Genetics and Conservation Ecology, as well as MS and PhD programs. The department's 24 faculty also support core facilities and natural history collections in addition to the Jornada Basin Long Term Ecological Research site and externally funded training programs. For more information see: **http://bio.nmsu.edu**.

Full details of the position (Requisition **#2013002155**) are available at **http://www.nmsu.edu/~personel/postings/faculty/**.

NMSU is an EEO/AA employer. All offers of employment are contingent upon the verification of information required by federal law, state law and NMSU policies/procedures, which may include the completion of a criminal history check.

PURDUE UNIVERSITY

The Department of Biochemistry at Purdue University, West Lafayette, Indiana invites applications for a tenure track faculty position at the Assistant or Associate Professor level. The search will be focused on identifying researchers addressing critical questions in mechanistic protein biochemistry including, but not limited to, enzyme structure/function relationships and metabolic pathway analysis in plants, microorganisms, or animals. Applicants whose research is enabled by approaches such as genomics and bioinformatics, single molecule analyses, synthetic biology or chemical biology will be of particular interest. The successful candidate will be expected to develop an internationally-recognized research program, interact with diverse faculty, staff and students across campus, demonstrate excellence in their teaching of graduate and/or undergraduate courses, and function as an active member of the department and university faculty.

The Department of Biochemistry is a small, interactive, and collegial community of faculty, staff and students who contribute significantly to the vibrant life science community of Purdue University. Our faculty participate in interdisciplinary programs in plant biology, genetics, bioinformatics, cancer, neuroscience, and biophysics. Support facilities are available for genomic analysis, metabolomics, protein mass spectrometry, NMR, X-ray crystallography, microscopy, and transgenic animal research. For more information see **www.biochem.purdue.edu**.

Applicants for assistant professor should have a Ph.D. or equivalent degree in biochemistry, biophysics, computational biology or a related field and at least two years of post-doctoral experience. Successful candidates should have a strong publication record, the potential to develop a vigorous, extramurally-funded research program, and a commitment to research and teaching excellence. Candidates at the associate professor level must have a track record of academic achievement and external funding in addition to the above. Applications should include a cover letter, curriculum vitae, two-page summary of research interests, one-page teaching statement and the names and contact information of three references. Applications should be submitted electronically to **biochemsearch@purdue.edu**. Screening of applications will begin **October 31, 2013** and will continue until the position is filled. A background check will be required for employment in this position.

Purdue University is an Equal Opportunity/Equal Access/Affirmative Action Employer fully committed to achieving a diverse workforce.

Chair • Department of Ecology and Evolution

STONY BROOK UNIVERSITY

Stony Brook University's Department of Ecology and Evolution is seeking an individual with an outstanding academic background in any field of ecology or evolutionary biology to serve as the Department Chair. The successful candidate should have internationally recognized research credentials, a track record of extramurally funded research, demonstrated commitment to excellence in research and teaching, and proven leadership skills in an academic environment. Applicants should present a compelling vision to guide the future trajectory of the Department, capitalizing on the new initiatives put forward by the Department and University. The successful candidate will teach graduate and/or undergraduate courses according to their area of expertise.

The Department is a dynamic and growing department in a Tier I, AAU university offering competitive teaching loads and startups. Information about Department faculty and our strong graduate training program is available at *http://life.bio.sunysb. edu/ee/.* Areas of strength in our program include population genetics, conservation ecology, molecular evolution and phylogenetics, evolutionary genomics, species interactions, invasion ecology, biogeography, mathematical ecology, and marine and freshwater ecology. The Department has recently benefited from new University initiatives that include faculty hiring in a cross-departmental human evolution major, and active involvement in a number of campus wide multidisciplinary cluster hires. SUNY2020 has reinvigorated Stony Brook University with increasing resources and a drive for academic excellence. The University is a member of the prestigious Association of American Universities and co-manager of nearby Brookhaven National Laboratory, a multidisciplinary research laboratory supporting world-class scientific programs utilizing state-of-the-art facilities. Stony Brook Medicine is Suffolk County's only academic medical center and tertiary care provider. Collaborations are also possible with Cold Spring Harbor Laboratories. The campus is close to marine and terrestrial research sites, including 50,000 acres of legally protected pine barrens and woodlands. While in the New York metropolitan area, Stony Brook is located on the North Shore of eastern Long Island, NY, with access to farmlands, vineyards, miles of beaches, and convenient access to the cultural resources of New York City.

Required: Applicants must hold a PhD in ecology, evolution, statistics or related field, and have demonstrated excellence in research and leadership. Applications are due September 30, 2013. Applicants should complete the Academic Jobs application process online at *https://academicjobsonline.org/ajo/jobs/2939*. The application process consists of: 1) State employment application, 2) cover letter detailing administrative leadership experiences and philosophy, 3) research and teaching experience, 4) résumé and 5) the names and contact details of three academic referees for recommendation. Electronic submission via *academicjobsonline* is strongly preferred.

For a full position description, application procedures, and to apply online, visit *https://academicjobsonline.org/ajo/jobs/2939*. Alternatively, applicants may submit the application materials by mail to: Douglas Futuyma, Chair of Search Committee
c/o Donna DiGiovanni, Assistant to Chair, Department of Ecology and Evolution
Life Sciences Building, Room 650, Stony Brook University, Stony Brook, NY 11794-5245

Stony Brook University

Stony Brook University/SUNY is an affirmative action, equal opportunity educator and employer.

DES MOINES UNIVERSITY

Faculty Position- Bacteriologist - Department of Microbiology and Immunology

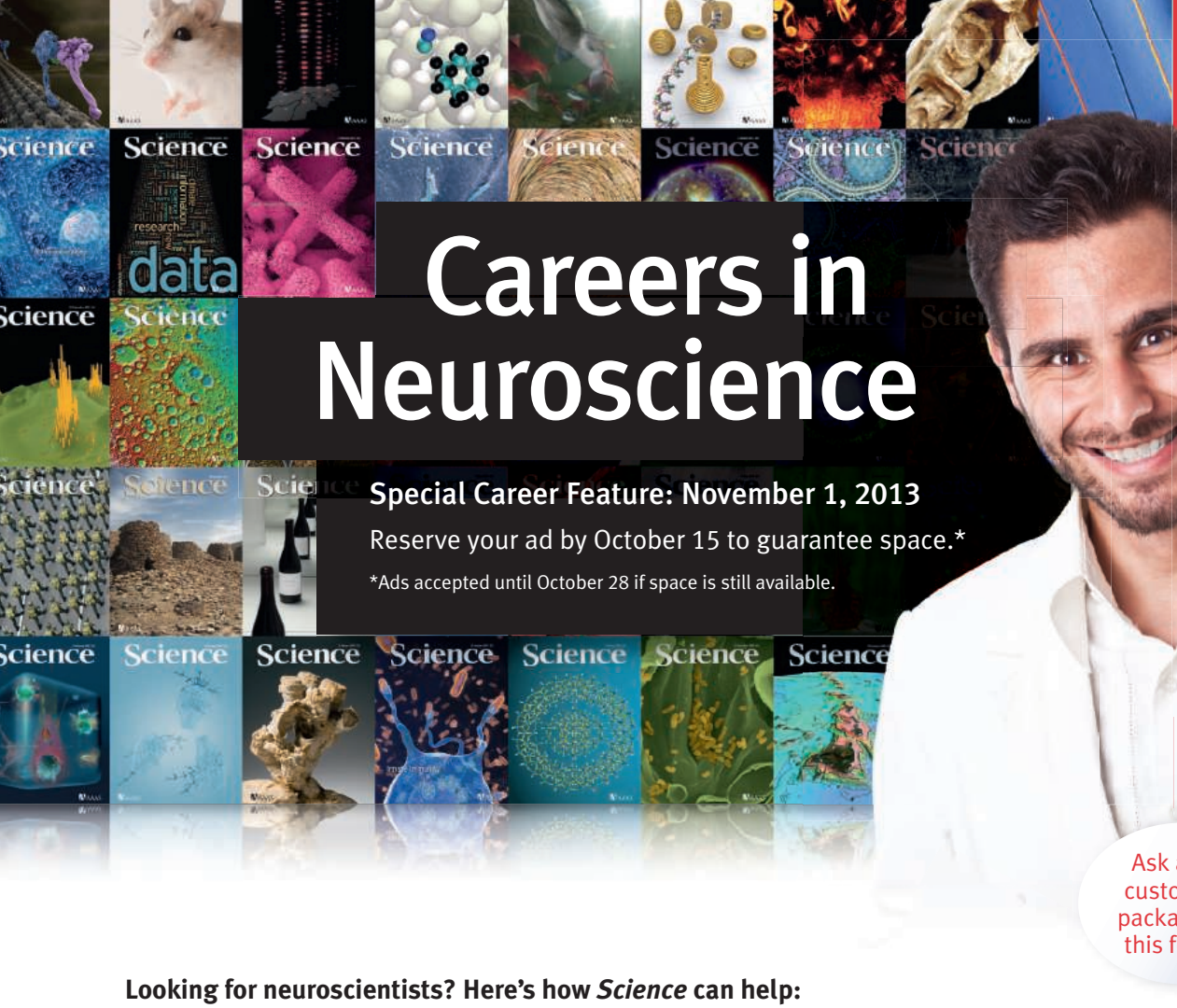
The Department of Microbiology and Immunology at Des Moines University invites applicants for a tenure-track position at the level of Assistant, Associate, or Full Professor dependent on qualifications. The successful candidate must possess the knowledge and skills necessary to participate in the teaching of medical bacteriology to medical and health professional students. In addition, candidates will be expected to teach, mentor, and train students in the Master's in Biomedical Sciences graduate program. Des Moines University is committed to advancing its research enterprise and fostering an environment conducive to individual and collaborative scholarly success. Therefore, desirable applicants will be able to demonstrate the potential to develop an innovative and extramurally funded research program in the area of medical bacteriology. Applicants should have a Ph.D. in microbiology or a related discipline and relevant postdoctoral experience. Compensation and lab start up costs are funded by the University and are not dependent on grant funding.

A proven record of achievement in medical or health professions education, and a history of extramural research funding are essential for appointment at the rank of Associate or Full Professor. Applicants are invited to submit their curriculum vitae, a concise statement of teaching interests and experience, a statement of research goals and objectives, and the names of three professional references using the online applicant tracking system at **www.dmu.edu/employment**. Review of applications will begin on or about **September 1, 2013** and continue until the position is filled.

Candidates with questions specific to this position may contact the Search Committee Chair, Andrew Brittingham, Ph.D. at Andrew.Brittingham@dmu.edu. For a complete job description, faculty benefits summary and/or information about Des Moines University, please visit **www.dmu.edu/employment**.

For more information on all that the Des Moines area has to offer regarding housing, schools, entertainment, cost of living and more, visit **www.desmoinesmetro.com**.

Des Moines University is an Equal Opportunity/Affirmative Action Employer. The University seeks excellence through diversity among its administrators, faculty, employees and students. The University prohibits discrimination on the basis of race, color, national origin, creed, religion, age, disability, sex, gender identity, sexual orientation, veteran status, genetic information or any other legally protected status. Applications by members of all underrepresented groups are encouraged.



Careers in Neuroscience

Special Career Feature: November 1, 2013

Reserve your ad by October 15 to guarantee space.*

*Ads accepted until October 28 if space is still available.

Ask about customized packages for this feature

Looking for neuroscientists? Here's how *Science* can help:

Content: This feature takes a look at sensory science to help understand the mechanisms underlying our perceptions. Researchers are working to help translate these basic research findings into innovations that improve how we experience life, from restoring hearing loss to dampening pain to enriching the scents and flavors of every day products.

Reach: 30% of our readers' primary work or interest = neuroscience. In the last quarter, over 6,700 job seekers were searching for Neuroscience positions on ScienceCareers.org. Make sure you are reaching these targeted groups by advertising in print and on our job board.

Bonus Distribution to:

- Society for Neuroscience, November 9–13, San Diego, CA
- Special Distribution to 25,000 scientists beyond our regular circulation

Results: When it comes to finding the right researcher, *Science* offers a simple formula: relevant content that spotlights your ad + a large, qualified audience = your hiring success.

Find your next hire in our November 1 Neuroscience feature.

To book your ad:

E-mail: advertise@sciencecareers.org

Or telephone us:

US/Canada/South America: 202-326-6582

Europe/India/Australia/New Zealand/ Rest of World: +44 (0) 1223 326500

Japan: +81-(0)90-9110-1719

China/Korea/Singapore/Taiwan/ Thailand: +86-1367-1015-294

For recruitment in science, there's only one Science

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From the journal *Science* AAAS

ScienceCareers.org

Produced by the *Science*/AAAS Custom Publishing Office

ETH

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Assistant Professor of Plant Cell and Developmental Biology /Plant-Microbial Interactions

The Department of Biology (www.biol.ethz.ch) in cooperation with the Department of Environmental System Sciences (www.usys.ethz.ch) at ETH Zurich invites applications for above-mentioned position. The new professor is expected to build a vibrant, world-class research program that combines state-of-the-art technologies in plant molecular cell biology, live cell imaging, and genetics to generate new knowledge of the fundamental molecular mechanisms underlying plant development and/or plant microbe interactions. The activities should be integrated with ongoing research developed in the Department of Biology in the areas of plant biology and genetics, cell dynamics, systems biology. The successful candidate is also expected to promote translational research activities in the context of the World Food System strategic initiative of ETH Zurich. He or she will be a member of the Department of Biology and associated with the Department of Environmental System Sciences and contribute to the teaching activities offered by these departments at the bachelor and master levels. The research group will be housed in the Institute of Agricultural Sciences. The new professor will be expected to teach undergraduate level courses (German or English) and graduate level courses (English).

This assistant professorship has been established to promote the careers of younger scien-tists. The initial appointment is for four years with the possibility of renewal for an additional two-year period.

Please apply online at www.facultyaffairs.ethz.ch

Applications should include a curriculum vitae, a list of publications, the names of at least three referees, a teaching statement, and a short overview of the research interests. The letter of application should be addressed **to the President of ETH Zurich, Prof. Dr. Ralph Eichler. The closing date for applications is 30 November 2013.** ETH Zurich is an equal opportunity and family friendly employer and is further responsive to the needs of dual career couples. In order to increase the number of women in leading academic positions, we specifically encourage women to apply.



Louisiana State University Health Sciences Center – Shreveport

Vice Chancellor for Research

The LSU Health Sciences Center in Shreveport, LA is seeking candidates for the role of Vice Chancellor for Research. The individual selected for this position will provide executive leadership for research administration and planning, and will work with fellow leaders to strengthen the campus research enterprise and infrastructure for an innovative and multi-disciplinary research program across North Louisiana.

The Vice Chancellor for Research will lead the institution in all areas of research. The Vice Chancellor will represent the campus in matters related to research including federal and state agencies, other research institutions and the local community. A priority for the incumbent will be to facilitate translational research opportunities. Additionally, the Vice Chancellor will be the designated Institutional Official responsible for research across the organization.

The institution's 436 bed University Hospital serves an urban and rural population of approximately 2.5 million, encompassing 25,000 square miles in Louisiana, East Texas, and Southwestern Arkansas. The resources for basic and clinical research are excellent. We have a long history of successful research collaboration between the basic science and clinical departments. The Virginia Shehee Biomedical Research Institute is ~160,000 total square feet and includes wet lab and staffed core facilities, such as for cellular imaging, DNA array analysis, and mass spectroscopy-proteomics. For more information on this opportunity at LSUHSC please visit us at ***http://www.lsuhscshreveport.edu/VCRworking Prospectus***

Successful candidates must be an MD/PhD or MD with an outstanding record of scholarly achievement, including a history of independent federal research funding, serving as a principal investigator and having administrative experience relevant to clinical and basic research. Requirements include an understanding of the diverse forms of research and scholarship conducted at a comprehensive research university, and an informed perspective about federally sponsored programs, intellectual property, technology transfer and commercialization in the university setting.

The search is being led by Glenn Mills, MD, FACP, Professor of Medicine, Chief, Section of Hematology and Oncology and Director, Feist-Weiller Cancer Center. Interested candidates may submit curriculum vitae via email at ***ShvFacultyRecruiting@lsuhsc.edu*** Materials that cannot be submitted electronically may be mailed to: Vice Chancellor for Research Recruitment, Human Resource Management, 1501 Kings Highway, Shreveport, LA 71103.

LSU Health Shreveport respects diversity in the workplace and is an Equal Opportunity Employer.

HARVARD UNIVERSITY
Psychology/Center for Brain Science
Faculty Search

The Department of Psychology, in conjunction with the Center for Brain Science, seeks faculty applicants whose research is focused on neurobiological approaches to human brain function. Areas of interest include, but are not limited to, perception, sensory and motor function, decision-making, biological bases of psychiatric disease, connectomics, and theoretical neuroscience. The successful appointee will be expected to strengthen links between the Department and the Center, where research focuses on the structure and function of neural circuits and their relationship to behavior. The appointment is expected to begin on July 1, 2014. Candidates at all levels are encouraged to apply.

Candidates should have demonstrated excellence in both research and teaching. Teaching opportunities will include offerings at both undergraduate and graduate levels. An appointment may be made at either the tenured or tenure-track (assistant or associate) levels.

Candidates for tenured positions should upload applications to:
http://academicpositions.harvard.edu/postings/4935
Candidates for tenure-track positions should upload applications to:
http://academicpositions.harvard.edu/postings/4933

Questions regarding this position can be addressed to **BrainSearch@wjh.harvard.edu**. The committee will begin considering completed applications on **November 15, 2013**.

Harvard University is an Affirmative Action/Equal Opportunity Employer, and we actively encourage applications from women and minority groups.

Stowers Institute for Medical Research
Faculty Position in the Life Sciences

The Stowers Institute for Medical Research invites applications for a faculty position in the Life Sciences. We anticipate making an appointment in 2014 at the rank of Assistant Investigator. Research programs of interest include, but are not limited to: computational biology, genomics, stem cell biology, regenerative biology, epigenetics, and cell biology. Our interests encompass a broad gamut of experimental organisms and approaches. The successful candidate will benefit from and complement the Institution's existing strengths in genetics and epigenetics, cell and chromosome biology, stem cells and regenerative biology, developmental biology and evolution, biochemistry and neuroscience.

The position is fully funded throughout the candidate's appointment. This includes $580,000 per year for full salary support and research funding, in addition to start-up funds and ongoing needs for equipment. The initial appointment is for 6 years and is then subject to renewal every 6 to 7 years. In total, the package for a junior position is more than $3.5 million over the first term and increases significantly after promotion. In addition, investigators may take advantage of exceptional Core facilities and technology centers staffed by over 100 scientists. Stowers investigators may also choose to teach or mentor predoctoral researchers from the Institute's Graduate School.

Candidates must have a Ph.D. or equivalent degree and postdoctoral experience demonstrating innovation and excellence in their field. Candidates will be expected to possess a long-term vision of their scientific interests, to establish a vigorous and innovative research program, and to actively contribute to the Institute's mission and collegiality.

Deadline for applications is **November 1, 2013**. Applicants should submit a CV, a research plan, and arrange for the submission of three letters of reference through our application page at: **http://www.stowers.org/facsearch2014/home**. Questions should be directed to the Search Committee Chair, Dr. Alejandro Sánchez Alvarado (**facultysearch@stowers.org**).

The Stowers Institute for Medical Research is proud to be an Equal Opportunity Employer.

University of Massachusetts Medical School
Tenure-Track Faculty Position
Department of Microbiology and Physiological Systems

The Department of Microbiology and Physiological Systems at the University of Massachusetts Medical School (http://www.umassmed.edu/) invites applications for a tenure-track faculty position at the rank of Assistant Professor. Depending on qualifications, candidates may be proposed for a more senior appointment at the rank of Associate or Full Professor. The Department is seeking candidates who can build on its core strengths in systems biology of infectious disease, immunology, virology, and cellular physiology. We are particularly interested in candidates with cross-disciplinary approaches to problems in bacterial or viral infection including, but not limited to: integrative/systems approaches to infection; analysis of complex microbial communities and their impact on the host; molecular mechanisms of pathogenesis; cell biology of infection; and host responses and adaptation to infection. Candidates will be expected to develop and maintain an innovative, externally funded research program. We offer generous support and a highly collaborative environment with opportunities for both basic and translational research. The position will be highly competitive with regard to start-up funds and salary.

Review of applications will begin on October 1, 2013 and continue until the position is filled.

Applicants should submit a cover letter explaining their interest in the Department, a curriculum vitae that includes honors and publications, and a succinct research plan to https://academicjobsonline.org/ajo/jobs/2924. To expedite the review process, applicants should invite three individuals who are familiar with their work and potential for success to upload recommendation letters at the same web address.

The University of Massachusetts Medical School is an equal opportunity and affirmative action employer that recognizes the power of a diverse community and encourages applications from individuals with varied experiences, perspectives and backgrounds.

Assistant Professor
Department of Biological Chemistry and Molecular Pharmacology
Harvard Medical School

The Department of Biological Chemistry and Molecular Pharmacology at Harvard Medical School invites applicants for a tenure-track faculty position at the rank of Assistant Professor. We are seeking individuals with a demonstrated potential for imaginative research and who propose to work on exciting problems in any area of chemical biology, structural biology, or single-molecule biochemistry. The successful candidate will be expected to direct innovative and independent research and participate in the teaching of graduate and/or medical students. Our highly interactive environment provides the opportunity to engage and collaborate with other dedicated researchers both within the Department and throughout the diverse Harvard research community. Significant scholarly and scientific resources will be made available for this appointment. For further information about our Department, please see our Web Page: **http://bcmp.med.harvard.edu**.

Applicants should submit electronic copies of their curriculum vitae, a description of research accomplishments and future research interests (three pages maximum), and ask at least three references to provide letters of recommendation.

These materials should be submitted using the following link:
https://academicpositions.harvard.edu/postings/4973
Applications will be considered starting November 1, 2013.

Harvard Medical School is an Equal Opportunity/Affirmative Action employer. We are actively committed to increasing the diversity of our faculty. Women and members of underrepresented minority groups are therefore strongly encouraged to apply.

HARVARD MEDICAL SCHOOL

Royal Society Research Professorship

The Royal Society's most prestigious funding scheme is now open for applications. The Royal Society Research Professorships provide long term support to world-class scientists, releasing them from teaching and administration to enable them to focus on research.

The scheme provides a substantial contribution to salary, which can be supplemented at the discretion of the host organisation; a one-off start-up grant of up to £35,000; and research expenses of up to £16,000 per academic year. Funding is available for five years, with the opportunity for renewal for a further five years.

These posts enable individuals of proven ability and achievement to undertake independent, original research at a UK institution. Former Research Professors include Presidents of the Royal Society and Nobel Laureates.

Several Royal Society Research Professorships are available. The number of awards made will be determined by the quality of applications received. The Professorships may be awarded in any field across the natural sciences but the following are restricted to specific areas:

- The Royal Society Wolfson Research Professorship in Physics or Chemistry at the interface with Biology
- The Royal Society GSK Research Professorship in Molecular aspects of Medicine
- The Royal Society Napier Research Professorship to ascertain the cause of cancer, including any corresponding allied disease and the means of prevention, cure and alleviation

Scientists of any nationality can apply and applications are particularly welcomed from scientists currently resident outside the UK.

Closing date: 13 March 2014

Host universities are encouraged to use the long lead time to identify and attract the best candidates. Fast-track applications will be considered during this period for truly exceptional overseas candidates.

To find out more visit
royalsociety.org/grants/schemes
or email **seniorfellowships@royalsociety.org**

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UMASS AMHERST

Tenure-Track Faculty Position in Immunology

The Department of Veterinary and Animal Sciences, University of Massachusetts at Amherst (https://www.vasci.umass.edu/), invites applications for a tenure-track position at the assistant professor level. The Department has a strong commitment to Veterinary and Biomedical Research and to Veterinary and Animal Science undergraduate and graduate education. It is housed in modern research facilities, has an interactive faculty with strength in immunology, reproduction and development and environmental toxicology, has excellent core facilities and is integrated into the University of Massachusetts life sciences research community.

Minimum Qualifications: Applicants must have a Ph.D., D.V.M./Ph.D., or M.D./Ph.D. and have developed or have the potential to establish a vigorous independent research program in one or more of the following areas of immunology: infectious and parasitic disease, autoimmunity, lymphoid and myeloid cell signaling, tumor or cancer immunology. Research with a translational component is considered an advantage, as is an interest in veterinary systems, but these are not required. The successful applicant will be expected to establish an extramurally funded research program and to contribute to undergraduate and graduate teaching and advising, consistent with the teaching responsibilities of our faculty.

Salary and start-up will be commensurate with qualifications and experience, and the University of Massachusetts provides an attractive fringe benefits package.

Please submit applications to: jpwright@vasci.umass.edu, subject line – Immunology Position. The application should be a single PDF (5 MB maximum) that includes: (1) a cover letter addressed to the Search Committee Chair, Professor Samuel Black, and providing names and contact information for three individuals who are willing to write letters of recommendation; (2) a curriculum vitae; (3) a research plan; and (4) a statement of teaching interests. Applications will be reviewed beginning October 18th, 2013. The position will remain open until filled, with an anticipated start date in 2014.

The Amherst Campus of the University of Massachusetts is part of the Five-College Consortium in the beautiful Pioneer Valley of Western Massachusetts. The University and town offer rich social and cultural life and diverse recreational amenities. We are 2 hours from Boston and 3 hours from New York City by car.

The University seeks to increase the diversity of its professoriate, workforce and undergraduate and graduate student populations because broad diversity is critical to achieving the University's mission of excellence in education, research, educational access and service in an increasingly diverse globalized society. Therefore, in holistically assessing many qualifications of each applicant of any race or gender we would factor favorably an individual's record of conduct that includes students and colleagues with broadly diverse perspectives, experiences and backgrounds in educational, research or other work activities. Among other qualifications, we would also factor favorably experience overcoming or helping others overcome barriers to an academic career or degree.

The University of Massachusetts Amherst is an Affirmative Action/Equal Opportunity Employer. Women and members of minority groups are encouraged to apply.

FACULTY POSITIONS Science Careers online @sciencecareers.org

SANFORD™
HEALTH

FACULTY POSITIONS AT ALL LEVELS SANFORD CHILDREN'S HEALTH RESEARCH CENTER SANFORD RESEARCH/USD

The Sanford Children's Health Research Center (CHRC, Sioux Falls, SD **http://www.sanfordresearch.org/researchcenters/childrenshealth/**), invites applications from researchers for full time faculty positions at the rank of Associate Scientist, Scientist, and Senior Scientist within Sanford Research/USD (**http://www.sanfordresearch.org/**) with commensurate rank of Assistant Professor, Associate Professor, and Full Professor in the Department of Pediatrics of the Sanford School of Medicine at The University of South Dakota. An historic $400 million gift by philanthropist Denny Sanford has allowed for expansion of Sanford Research/USD and development of the CHRC, a center specifically focusing on children's health research.

We seek outstanding scientists with research programs that contribute to the molecular understanding and treatment of congenital defects, developmental disorders, and pediatric diseases. Scientists with research projects relevant to type 1 diabetes are highly encouraged to apply. Applicants should hold a PhD, MD or MD/PhD degree and complement the existing strengths and the interdisciplinary and collaborative nature of the CHRC. Junior candidates will be expected to develop independent research programs with extramural funding. Senior candidates should have a demonstrated track record of extramural grant support and publications and be capable of providing mentorship to junior faculty members within the CHRC while advancing their independent research programs. Researchers will join the energetic and collegial research community at Sanford Research/USD and hold both Sanford Research/USD and Sanford School of Medicine faculty appointments.

Significant institutional support, including modern laboratory space and state-of-the-art facilities, will be provided in the Sanford Center. In addition, a comprehensive compensation package will be tailored to the individual's qualifications. Sanford Health is an Equal Opportunity/Affirmative Action Employer. Candidates should submit a single PDF including a detailed *curriculum vitae* and a description of research experience and future plans that includes relevance to children's research. Candidates should also submit at least three letters of recommendation. All application materials should be sent by email to:

David A Pearce Ph.D.
Director, Children's Health Research Center
Sanford Research/USD
Professor, Department of Pediatrics
Sanford School of Medicine of The University of South Dakota
2301 E. 60th Street North
Sioux Falls, SD 57104
Telephone: 605-312-6004
FAX: 605-312-6071
Email: David.Pearce@sanfordhealth.org

UNIVERSITY of ROCHESTER

JAMES P. WILMOT CANCER CENTER ENDOWED PROFESSORSHIP AND LEADER OF HEME-MALIGNANCY RESEARCH PROGRAM

ROCHESTER, NY

The James P. Wilmot Cancer Center at the University of Rochester Medical Center (URMC) seeks an outstanding senior investigator with a strong interest in both basic and translational research on heme-malignancies/hemapoietic stem cells to lead its heme-malignancy research program.

The successful applicant will enjoy a multi-disciplinary and highly interactive research community at URMC with vibrant graduate programs and state of the art infrastructure and core facilities. Laboratory space will be provided on the research floor of the James P. Wilmot Cancer Center building completed in 2008. Affiliation with an academic department will be offered according to the best fit.

Candidates for this position must hold a Ph.D. and/or an M.D. and must qualify for the rank of full professor at the University of Rochester. Desirable candidates will have a distinguished research record and a strong active and federally-funded research program. S/he will have a demonstrated record of mentorship and collaboration.

The university has retained Isaacson, Miller, a national executive search firm, to assist with this important search. All inquiries, nominations, and resumes with cover letters may be submitted in confidence to: **Heather Brome, Senior Associate, Isaacson, Miller, E-mail:4861@imsearch.com, Phone: 617.262.6500**

The University of Rochester is an Equal Opportunity Employer and women and minorities are encouraged to apply.

ISAACSON, MILLER
www.imsearch.com

Faculty Positions Infectious Diseases Research

The Public Health Research Institute (PHRI) of Rutgers New Jersey Medical School in Newark, New Jersey, is recruiting new faculty members at the middle or senior level to join a growing group of 23 laboratories. PHRI (www.phri.org) is a leading infectious diseases research center that emphasizes basic and translational sciences. Candidates must have training and experience of the highest quality, and a NIH-funded research program addressing critical questions in cell biology, immunology and molecular biology that offer novel insights into pathogenicity, as well as innovative approaches for new vaccines, therapeutics and diagnostics. The PHRI Center is housed in a state-of-the-art research facility that has extensive core services, including nationally designated BL3 laboratory and animal facilities, X-ray facility for structural studies and applied genomics center. The PHRI Center offers a robust and highly collegial research environment, generous start-up funds, and a comprehensive benefits package. Candidates should submit a curriculum vitae, a statement of research interests and accomplishments and a list of at least three references, to: **Dr. Issar Smith, Public Health Research Institute, Rutgers New Jersey Medical School, 225 Warren Street, Newark, NJ 07103; Phone: (973) 854-3260; Fax: (973) 854-3101; E-mail: smithis@njms.rutgers.edu**.

Please note that effective July 1, 2013, as a result of the New Jersey Medical and Health Sciences Restructuring Act, several units from the former University of Medicine and Dentistry of New Jersey (UMDNJ) are now part of Rutgers Biomedical and Health Sciences (RBHS). For the purposes of payroll and benefits administration, the above position is a legacy UMDNJ position at Rutgers, and is eligible for benefits associated with legacy UMDNJ positions.

Rutgers, the State University of New Jersey, is an Equal Opportunity / Affirmative Action employer, and is compliant with the Americans with Disabilities Act (ADA). For more information, please visit http://jobs.rutgers.edu/TheRUCommitment.htm

RUTGERS
New Jersey Medical School

Tenure Track Assistant Professor University of Michigan Astrobiology

The Departments of Astronomy and Biophysics at the University of Michigan anticipate that a tenure track faculty position will be available with a September 2014 starting date. The position is an Assistant Professorship with a university year appointment. Appointment at a higher rank may be considered for candidates with an exceptional record of productivity. We are considering applications in all areas of astrobiology, broadly defined, especially those areas focused on the origin of life. Information about our research areas can be found at **http://www.lsa.umich.edu/astro/** and **http://www.lsa.umich.edu/biophysics**. Candidates are required to have a doctoral degree in one of or more relevant areas, which are biophysics, astronomy, chemistry, or physics. The successful candidate is expected to establish an independent research program and to contribute effectively to our undergraduate and graduate teaching programs. Applicants should submit a curriculum vitae, a brief statement of present and future research plans, a statement of teaching philosophy and experience, at least three letters of recommendation, and evidence of teaching experience, if any. The deadline for applications is **November 1, 2013**. Applications can be submitted to **http://www.lsa.umich.edu/biophysics**. If you should have any questions, please feel free to contact Ann Titus at **atitus@umich.edu** or **(734) 764-1146**.

Women and minorities are encouraged to apply. The University of Michigan is supportive of the needs of dual career couples and is an Equal Opportunity/Affirmative Action Employer.

Florida State University

Strategic Faculty Recruitment in Energy and Materials

Florida State University is continuing its *major interdisciplinary initiative in the areas of Energy and Materials*. During the 2013-14 academic year the University will be recruiting as many as nine tenure-track/tenured faculty members to supplement the three faculty hired last year in these areas. This search is open with respect to rank and academic department. Successful candidates are expected to have a synergistic impact on existing research programs in the University's departments and interdisciplinary centers as well as develop new areas. Sustained pursuit and growth of collaborative, externally-funded research programs is an explicit goal.

We invite applications from researchers active in the broadly-defined area of materials science and materials engineering with an emphasis on, but not restricted to, materials for energy production, conversion, storage and utilization. Target research areas in this search encompass theory, computation, synthesis including molecular, macromolecular and inorganic, thin films and crystals, biomaterials, fundamental characterization, materials measurement, device construction and proof of concept testing and prototyping. Successful candidates will be offered highly competitive salaries and start-up packages, state-of-the-art research space and access to world-class instrumentation, computing and facilities in academic and interdisciplinary units.

Related strengths at Florida State University include programs in Biological Science, Chemistry and Biochemistry, Physics, and Scientific Computing in the College of Arts and Sciences, and in Chemical and Biomedical, Electrical and Computer, Industrial and Manufacturing and Mechanical Engineering in the College of Engineering. Complementing these programs are interactive centers including the National High Magnetic Field Laboratory, the Applied Superconductivity Center, the High Performance Materials Institute, the Aero-Propulsion, Mechatronics and Energy Center, and the Center for Advanced Power Systems. Linking these colleges and centers is a new Ph.D. program in Materials Science and Engineering complementing robust department-based doctoral programs in materials and related areas.

Florida State University is classified as a very high research activity, doctorate-granting institution with a student population approaching 42,000. In recent years, the University has made considerable investments in research infrastructure in the sciences and engineering disciplines. The University is located in Tallahassee, the capital of Florida, where residents have access to a broad range of cultural amenities afforded by the presence of three institutions of higher learning. The region boasts an abundance of springs, lakes and rivers as well as pristine beaches on the Gulf of Mexico.

Applicants are asked to provide *a single document* in pdf format containing a letter of application including the names and contact information of three professional references, curriculum vitae, and a two page narrative describing their research interests that should include a clear statement as to how the candidate would complement this inter-college effort at Florida State University. Applications must be sent electronically to **materials2013.search@fsu.edu**. Review of applications will begin on **November 1, 2013**. Additional information about the related programs at FSU and this faculty search can be obtained at **http://www.research.fsu.edu/materials_search/**.

Florida State University is committed to the diversity of its faculty, staff, and students, and to sustaining a work and learning environment that is inclusive. Women, minorities, and people with disabilities are strongly encouraged to apply. FSU is an Equal Opportunity/Access/Affirmative Action Employer.

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MARCH 30 – APRIL 2
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Organizers: Loren Looger, Carlos Portera-Cailliau, Yi Zuo

APRIL 6 – 9
HOW TO READ A MAP: UNDERSTANDING STRUCTURE-FUNCTION RELATIONSHIPS IN THE BRAIN
Organizers: Vivek Jayaraman, Minoru Koyama, May-Britt Moser

APRIL 27–30
STRUCTURE AND FUNCTION OF THE INSECT MUSHROOM BODY
Organizers: Sarah Farris, Gerry Rubin, Glenn Turner

MAY 18 – 21
GENETIC MANIPULATION OF NEURONAL ACTIVITY III
Organizers: Peter Hegemann, Loren Looger, Julie Simpson

Janelia conferences are small, specialized events intended to encourage rapid scientific advances and foster collaborative interactions.

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Careers in China

Special Career Feature: November 15, 2013

Reserve your ad by October 29 to guarantee space*

*Ads accepted until November 11 if space is still available.

Here's why you should advertise in this issue:

Content: The November 15 issue of *Science* includes a special feature on China. The feature will focus on opportunities for Chinese students/scientists to grow their careers in China as well as opportunities for foreigners within China to advance their education and scientific training.

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Science Careers
From the journal *Science* AAAS

ScienceCareers.org

* * Publisher's Own Data, August 2012

Produced by the *Science*/AAAS Custom Publishing Office

Tenure-Track Assistant Professorship in Chemistry (Organic) Harvard University

Candidates are invited to apply for a tenure-track assistant professorship in organic chemistry, broadly defined to include chemical biology, organic synthesis, organic materials, physical-organic chemistry, organometallic chemistry, and catalysis. The appointment is expected to begin on July 1, 2014. The tenure-track professor will be responsible for teaching at the undergraduate and graduate levels. We are seeking candidates who have an outstanding research record and a strong commitment to undergraduate and graduate teaching. Doctorate required by expected start date.

Candidates should arrange to have three letters of recommendation sent independently and provide a curriculum vitae, statement of teaching philosophy, list of publications, and outline of their future research plans. All applications and supporting materials must be submitted via the ARIeS portal (**http://academicpositions.harvard.edu/postings/4914**) no later than **October 15, 2013**.

Harvard is an Equal Opportunity/Affirmative Action Employer. Applications from women and minorities are strongly encouraged.

Department of Chemical Sciences, Assistant Professor (Materials Chemistry, full-time, tenure-track)

The Department of Chemical Sciences at Bridgewater State University invites applications for a new full-time, tenure track assistant professorship in Materials Chemistry beginning in September 2014. The successful candidate will have a strong commitment to excellence in undergraduate teaching (including introductory and upper level inorganic or physical chemistry courses), and in developing a research program appropriate to an undergraduate setting (**http://www.bridgew.edu/OUR/**). Excellent teaching and research facilities are available in our new $98.5M Science and Mathematics Center.

Required Minimum Qualifications: A Ph.D. and post-doctoral experience in either physical chemistry or inorganic chemistry with an emphasis in materials chemistry are required, as are excellent oral and written communication skills.

Preferred Qualifications: Prior college level teaching experience is preferred. Candidates with a background in one or more of the following areas are encouraged to apply: sustainable materials, novel electronic or magnetic materials, materials for energy storage and conversion, biomaterials, and nanostructured materials.

Special Instructions to Applicants: For consideration, submit electronically a letter of application, curriculum vitae, and statements of teaching philosophy and research plans at **http://jobs.bridgew.edu**

Review of complete applications will begin on October 15, 2013 and continue until the position is filled.

Bridgewater State University is an affirmative action/equal opportunity employer which actively seeks to increase the diversity of its workforce.



Scan QR Code for more information.

BRIDGEWATER STATE UNIVERSITY

For a complete listing of all available positions, and to apply online visit
http://jobs.bridgew.edu

BioTechMed GRAZ



BioTechMed-Graz is a cooperative initiative between the University of Graz, the Medical University of Graz and the Graz University of Technology at the interface of basic biomedical research, technological developments and medical applications.

With the cooperative project BioTechMed-Graz, the three partner universities are pursuing the goal of pooling their pre-existing competences in the four major research areas of 'Molecular Biomedicine', 'Neurosciences', 'Pharmaceutical and Medical Technologies' and 'Quantitative Biomedicine and Modelling'. To strengthen the cooperation, four junior research groups in the above-mentioned research areas will be implemented.

The following § 99 (1) UG professorships are to be filled:

Professorship of Neuroimaging –
Institute of Psychology at the University of Graz

Professorship of Interactive Microbiome –
Medical University of Graz

Professorship of Biopharmacy – Graz University of Technology

Professorship of Bioinformatics – Graz University of Technology

Necessary Qualifications:
- University degree in the subject area
- Scientific doctorate or relevant habilitation or equivalent qualification
- Pedagogical aptitude for university teaching
- Experience holding lectures in English is advantageous
- Competence in the field of gender mainstreaming
- International research activities
- Experience in the successful acquisition of third party funds
- Excellent publication record

40 hours/week; 5 year limited term employment contract according to § 99 (1) UG; expected to be filled starting February 1st 2014

Date for interviews and lectures of potential candidates:
21–23 November 2013

End of application deadline: **10 October 2013**

Link for further information: ***http://biotechmedgraz.at/de/***

AgreenSkills
Pathways for inventive researchers

AgreenSkills Post-doctoral Research Fellowships

Next application deadline: 15 November 2013

AgreenSkills is an excellence-oriented programme, accepting applications for post-doctoral fellowships from international researchers, at the early stages of promising careers, in the fields of **life**, **agricultural**, **nutrition**, and **environmental sciences**. Proposals are accepted, without any topic guideline, for **basic or applied sciences**.

Incoming fellows are offered 1-2 year positions in France at one of Agreenium's member organizations (INRA, Cirad, AgroParisTech, Agrocampus Ouest, Montpellier SupAgro, and INPT-ENVT); while, outgoing fellows, already employed by an Agreenium member, spend their 6-24 month mobility period at an institution outside France.

As a European Commission co-funded mobility programme, AgreenSkills strives to offer its fellows **competitive salary and career development packages**, within first-rate research environments. Each fellowship is tailored to the needs of the fellow, with a particular focus on training, networking, and flexibility.

AgreenSkills has a continuous call for submissions, with the next evaluation deadline on the 15th of November 2013.

contact@agreenskills.eu/ www.agreenskills.eu

European Commission | INRA | agreenium

CALIFORNIA STATE UNIVERSITY, FULLERTON
BIOANALYTICAL and BIO-ORGANIC CHEMISTRY

The Department of Chemistry and Biochemistry at California State University, Fullerton invites applications for two full-time, tenure-track positions preferably at the Assistant Professor level with expertise in **BIOANALYTICAL CHEMISTRY** and in **BIO-ORGANIC CHEMISTRY**.

Applicants shall have a Ph.D. in the appropriate area of chemistry as well as relevant postdoctoral experience. We are particularly interested in candidates whose research interests complement the department's existing research programs or further expand research opportunities at the interface of chemistry and biology. The candidates will be expected to maintain an active, externally funded research program involving undergraduate and M.S. students, and be committed to excellence in teaching and mentoring a diverse student population. Teaching responsibilities will include undergraduate and graduate level lecture and lab courses in their area (e.g. analytical or organic chemistry) as well as lower division courses (e.g. general chemistry). The following required application materials must be submitted as pdf documents: (a) cover letter, (b) curriculum vitae, (c) a statement of teaching philosophy and experience that addresses teaching diverse populations (3 page limit), (d) a statement of research plans that addresses projects to engage undergraduate and M.S. students (4 page limit), (e) copies of relevant peer-reviewed publications, (limit of 3), and (f) names and contact information for 3 individuals who will send letters of recommendation. The recommenders are required to directly send a signed letter of recommendation on official letterhead stationery either via email or by mail. For more information on the two positions and for complete application instructions, email and mailing addresses, please visit **http://chemistry.fullerton.edu/employment.asp**.

Review of applications will begin **October 15, 2013** for the bioanalytical position and **November 1, 2013** for the bio-organic position and will continue until the positions are filled.

California State University, Fullerton is an Equal Opportunity/Title IX/503/504/VEVRAA/ADA Employer.

THE UNIVERSITY OF KANSAS
THEORETICAL CHEMISTRY FACULTY POSITION

The Department of Chemistry at the University of Kansas is seeking exceptional candidates for a tenure-track position in Theoretical/Computational Chemistry at the assistant or associate professor level, expected to begin as early as August 18, 2014. The successful candidate will help to realize the Department's goal of enhancing research expertise in the area of materials chemistry, broadly defined, while complementing the existing strengths of the department. The University of Kansas is especially interested in hiring faculty members who can contribute to four key campus-wide strategic initiatives:

- Sustaining the Planet, Powering the World;
- Promoting Well-Being, Finding Cures;
- Harnessing Information, Multiplying Knowledge; and
- Building Communities, Expanding Opportunities.

See **www.provost.ku.edu/planning/themes/** for more information. A desire to effectively teach at both the undergraduate and graduate levels is expected and a statement of teaching philosophy and interests is required. A competitive salary will be offered that is commensurate with experience. A PhD in chemistry or a closely related field is expected by the start of appointment and postdoctoral experience is desirable.

For a complete announcement and to apply online, go to **https://employment.ku.edu** and click "Search Faculty Jobs" and search openings by keyword "Chemistry". Submit online an application cover letter, CV, contact information for three references, statement of teaching interests, and a description of research plans. In addition, arrange for three letters of recommendation to be sent separately to **Elaine Knight, Theory Search Committee Coordinator, Department of Chemistry, Malott Hall, 1251 Wescoe Hall Drive, University of Kansas, Lawrence, KS 66045 (eknight@ku.edu; 785-864-5206)**. Review of applications will begin **October 1, 2013**, and will continue as long as needed to identify a qualified pool.

EOE M/F/D/V

UNIVERSITY OF CENTRAL FLORIDA
College of Medicine

Orlando, FL

Director of the Burnett School of Biomedical Sciences (BSBS)

The College of Medicine at the University of Central Florida (UCF) in Orlando, Florida invites applications and nominations for the position of **Director of the Burnett School of Biomedical Sciences (BSBS)**. The mission of BSBS is to provide quality undergraduate and graduate programs in biomedical sciences and build excellent research programs focused on cancer, cardiovascular, neurological, and infectious diseases. BSBS seeks an accomplished academician and researcher with a Ph.D. or Ph.D./M.D. in a discipline appropriate to the school and a distinguished record of research, scholarship, and professional accomplishments that would merit appointment as a Professor with tenure. The director must have a strong commitment to graduate, undergraduate and professional education, significant active extramural funding, experience in successfully recruiting and mentoring faculty, and administrative experience in a university setting. Candidates should also possess strong interpersonal and leadership skills, demonstrable organizational and strategic planning skills, experience in a diverse interdisciplinary environment, and a record of community partnerships and resource development. BSBS is part of a well-planned medical city with adjacent shopping areas and pleasant residential areas. Orlando is a dynamic and progressive metropolitan region, a major player in high-tech industry, and a great place to live and work.

Witt/Kieffer has been retained by the University of Central Florida College of Medicine, Burnett School of Biomedical Sciences to assist in this recruitment. Inquiries, nominations and applications are invited. Applications should include a curriculum vitae, cover letter, and the names of three references (who will not be contacted without permission). The documents should be submitted electronically to UCFBSBS@wittkieffer.com. Inquiries may be addressed to Anne Zenzer or Lisa Flavin, the Witt/Kieffer consultants supporting this search, at 781-272-8899. Applications will be accepted until the position is filled.

UCF is an equal opportunity, affirmative action employer and especially encourages the candidacies of women, members of racial and ethnic minorities, and persons with disabilities. All searches and documents are subject to the Sunshine and public records laws of the State of Florida.

WITT / KIEFFER

VCU

The Department of Anatomy and Neurobiology, School of Medicine, Virginia Commonwealth University is offering two tenure-track/tenured positions (F19890/F56750) at the Associate or full Professor level. The Department currently has 18 full-time neuroscience faculty. Internationally recognized research programs in **glial cell biology, neuroplasticity, and traumatic brain injury** are supported by substantial extramural funding. Additionally, the Department/VCU offers:

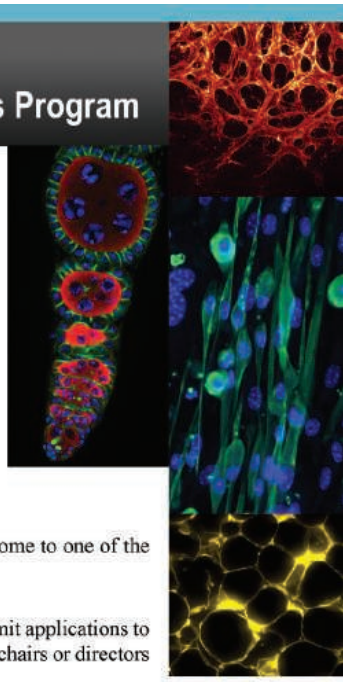
- An advanced, NIH-supported, bioimaging core housed within the department
- Multiple, staffed core facilities/centers (Center for Molecular Imaging, Flow Cytometry Resource Core, Chemical and Proteomic Mass Spectrometry Facility, Transgenic/Knock-out Mouse Facility, Cytogenetics Diagnostic Facility, and others)
- Positions that are supported by state funds
- Attractive and competitive salary and start-up funds

There is a large, active, and highly collegial neuroscience community at VCU that offers outstanding opportunities for collaborations with faculty in both basic science and clinical departments. Applicants should have an active and productive research program that complements the research directions of the department, and which is supported by significant extramural funding. The successful candidate will contribute to graduate and/or professional student teaching in either gross anatomy, histology, or neuroscience. Applicants should possess a PhD, MD, or DDS degree, or equivalent, and be committed to working with and fostering the development of a diverse faculty, staff, and student population or a commitment to do so as a faculty member at VCU. Review of the applications will begin immediately and the positions will remain open until filled.

Interested candidates should send a curriculum vitae, a one page letter of intent outlining their research and scholarly accomplishments, and the name, address, telephone number, and email address of three references. Application materials must be electronically submitted to **anatrecruit@vcu.edu**.

Virginia Commonwealth University is an Equal Opportunity/Affirmative Action Employer. Women, minorities, and persons with disabilities are encouraged to apply.

University of Texas Southwestern Medical Center
Assistant Professor Positions supported by the Endowed Scholars Program



THE ENDOWED SCHOLARS PROGRAM provides ***exceptionally generous start-up support, research space, salary and benefits*** for new Assistant Professors. The program, now in its 16th year, has launched the careers of a cadre of 74 investigators, who comprise a supportive network of institutional colleagues.

The Endowed Scholars Program gives early-career investigators the ***chance to tackle new and innovative research problems and take risks***, supported by the mentoring of distinguished senior scientists. Up to five new scholars are selected each year. Each scholar is appointed as a tenure-track assistant professor in a UT Southwestern basic science or clinical department.

UT Southwestern has vibrant medical and graduate schools. Endowed Scholars have ***access to graduate training programs and 18 Core Facilities***. The core facilities include DNA sequencing and bioinformatics services; electron microscopy; live-cell imaging; mouse gene knockout and transgenesis, metabolic and behavioral phenotyping; and structural biology.

A state-of-the-art high throughput chemical screening facility is available on campus. UT Southwestern is also home to one of the nation's first 7-Tesla magnetic resonance imaging devices for human studies.

Endowed Scholar positions are restricted to new first-time Assistant Professors. Interested individuals should submit applications to a Chair or Director of one of UT Southwestern's basic or clinical academic departments or research centers. Those chairs or directors then forward finalists' materials for consideration to the medical center's Endowed Scholars Committee.

For detailed information about nomination materials and currently available positions, please visit our Web page: www.utsouthwestern.edu/endowedscholars

UT Southwestern is an Affirmative Action/Equal Opportunity Employer.
Women, minorities, veterans and individuals with disabilities are encouraged to apply.

UT SOUTHWESTERN MEDICAL CENTER

University of Michigan
Medical School

Department of Computational Medicine and Bioinformatics
Assistant, Associate and Full Professors

The Department of Computational Medicine and Bioinformatics at the University of Michigan Medical School seeks outstanding applicants for tenure-track and tenured clinical and biomedical informatics faculty positions. UM hosts a Clinical and Translational Sciences Award (CTSA) and tranSMARTFoundation.org, a world-wide integrative biomedical informatics platform open-science activity. DCM&B has NIGMS bioinformatics and NCI proteome informatics pre-doctoral T32 training grants. We have active national outreach for minority candidates, in partnership with the NIH Research Centers for Minority Institutions (RCMI) program.

We are currently recruiting up to 2 senior and 2 junior faculty members to establish independent individual and team-based research programs. We have 10 primary, 8 joint, and 100 affiliate faculty members; we have50 current Ph.D. and 17 current MS students. We have 50 Ph.D. alums. Informatics research teams are also welcome to apply as a unit. Recruitments in the areas of basic bioinformatics and computational biology and the more applied biomedical/clinical informatics specialties are encouraged to apply. Specific joint appointments may be considered, for appropriate candidates, with the Dept. of Human Genetics, Electrical Engineering and Computer Science, School of Information, School of Public Health, School of Nursing or other appropriate units. In addition, affiliation with Centers, including the Comprehensive Cancer Center, Depression Center, Cardiovascular Center and Metabolomics and Obesity Center will be encouraged. There are extensive computational and information infrastructural resources are available to individual recruits and teams. For appropriate individuals, opportunities exist for faculty leadership roles in Research Information Technology management and operations and to influence institutional priorities in clinical and biomedical informatics.

Successful candidates will have a PhD and/or MD degree, or equivalent, with post-doctoral training, on topics such as biomedical data mining and machine learning; multi-scale integrative analysis; natural language processing (NLP) and ontologies applied to biomedicine; informatics related to healthcare delivery and personalized medicine (e.g. clinical decision support or pharmacogenomics). Publications and funding, as evidence of research productivity, a detailed research plan as well as evidence for an interest in in graduate and post-doctoral education will be essential components of the application. The rank of selected candidates will depend upon experience and qualifications.

Applicants should send a letter of interest with Curriculum Vitae, Research Plan, and a list of three or more references with current contact information to:**Search Committee, Department of Computational Medicine and Bioinformatics, Job Code 200. The University of Michigan, 2017 Palmer Commons, 100 Washtenaw Ave, Ann Arbor, MI. 48109-2218, email: ccmbrecruit@umich.edu. Applications will be reviewed through March 2014 beginning September 2013**.

Ann Arbor is a remarkable cultural and living environment. The University of Michigan is responsive to the needs of dual career families and is an Equal Opportunity Affirmative Action Employer committed to diverse faculty, staff and student body.

http://ccmb.med.umich.edu

Position Announcement – Small Grains Breeding & Quantitative Genetics

PURDUE UNIVERSITY

Small Grains Breeding and Quantitative Genetics Professor (OIE 002879-2013), Purdue University, Department of Agronomy, 915 West State Street, West Lafayette, IN 47907-2054. Tenure track position. Assistant Professor (academic 10-month appointment will include research (majority) and teaching). **Responsibilities:** The successful candidate is expected to develop an extramurally funded, internationally recognized, scholarly research program that utilizes modern plant breeding approaches for small grain crop improvement. The successful candidate must also be committed to teaching undergraduate and/or graduate courses in plant breeding and quantitative genetics, mentoring of undergraduate and graduate students, and fostering diversity. Specific research foci shall include small grain germplasm enhancement and variety development, trait development that may involve novel applications of molecular biology and quantitative genetics for crop improvement, and development of improved methodologies for plant breeding and phenotyping (e.g. yield, stress tolerance, flour quality). Although previous research experience in small grains breeding/genetics is desired, quantitative geneticists with excellent research accomplishments in other species are encouraged to apply. The successful candidate will develop and foster collaborations with researchers in small grains research and crop improvement at Purdue University and in the seed industry as well as other state, national and international crop improvement programs (e.g. http://tinyurl.com/purdueag; http://tinyurl.com/ARSPurdue; http://tinyurl.com/AgSeed). **Qualifications:** An earned Ph.D. in plant breeding or related discipline such as agronomy, plant breeding, genetics, biology, or molecular biology is required. Postdoctoral experience is desirable as is an interest and/or experience in the international dimensions of crop genetics.

The College: The College of Agriculture at Purdue University is deeply committed to the three land-grant missions (teaching, research, and Extension), to international activities and perspectives that span all missions, and to advancing diversity in all areas of faculty effort. The College has 11 academic departments and includes 320 faculty, 2650 undergraduate students, and 690 graduate students. Purdue Extension is comprised of campus specialists who partner with a statewide system of 270 professionals in all 92 counties delivering high-impact research-based programs to stakeholders in Indiana and around the world. The College's strategic plan can be accessed at http://www.ag.purdue.edu/Pages/strategicplan.aspx.

Applications: Review of applications will begin **October 15, 2013** and continue until a successful candidate is identified. A background check is required for employment in this position. Candidates must submit a letter of application, including a statement of research goals, teaching philosophy, curriculum vitae and contact information for four references (names, addresses, email addresses, telephone numbers) to: **Mitch Tuinstra (c/o Jenny Kelly - jckelly@purdue.edu), Department of Agronomy, Purdue University, 915 West State Street, West Lafayette, IN 47907-2054, Phone: 765-494-4774. URL: https://ag.purdue.edu/agry/**.

Purdue University is an Equal Opportunity/Equal Access/Affirmative Action Employer fully committed to achieving a diverse workforce.

Pomona College

PLANT PHYSIOLOGY

The Biology Department invites applications for a tenure-track position at the level of Assistant Professor in the area of Plant Physiology, beginning July 1, 2014. Pomona College, the founding member of the Claremont Colleges, is a highly selective liberal arts college attracting a diverse national student body. Candidates must have a Ph.D. and postdoctoral experience. Teaching responsibilities will include an introductory course in Cellular Chemistry and Cell Biology and an upper-level laboratory course in Plant Physiology. The appointee will be expected to initiate and sustain a productive research program that involves undergraduates. Please submit the following application materials online (**https://academicjobsonline.org/ajo/jobs/2899**): (a) cover letter, (b) curriculum vitae, (c) three statements — one addressing teaching philosophy, including a brief plant physiology course description, one addressing research plans, and one addressing personal commitment to mentoring a diverse student body, and (d) three letters of reference. You may address your cover letter to Prof. Daniel Martínez, Chair of the Search Committee. Complete applications received by **October 7, 2013** will receive full consideration.

The Biology Department supports equal access to higher education and values working in a richly diverse environment. The ideal candidate will have experience working with students from diverse backgrounds and a demonstrated commitment to improving higher education for underrepresented students.

UNIVERSITY of TORONTO

The Joint Postdoctoral Fellowship of the Dr. Charles H. Best and The Banting Research Foundations will be awarded this year to a highly qualified graduate (2 years or less postgraduate) in the field of molecular, genetic and genomic research. Applicants must address their applications to members of the Banting and Best Department of Medical Research (BBDMR) at the University of Toronto. Individual research programs include studies on gene regulation, signal transduction, development, systems biology, proteomics and functional genomics and are carried out in the new, state-of-the-art Donnelly Centre (**www.thedonnellycentre.utoronto.ca**).

Applications should be addressed to one or two BBDMR department members (Andrews, Bader, Blencowe, Boone, Brudno, Caudy, Emili, Fraser, Greenblatt, Hughes, Kim, Krause, MacLennan, Moffat, Morris, Roth, Ryu, Sidhu, Wheeler, Zhang), whose interests match their own. Upon agreement of sponsorship, the applicant must send a curriculum vitae, one page statement of research interests, transcripts, and three letters of reference to their sponsoring Faculty mentor. The deadline for applications is **October 25, 2013**. The successful applicant will be supported for up to two years with a generous stipend.

For additional information please visit:
www.utoronto.ca/bantresf/ and
www.charlesbestfoundation.ca

VANDERBILT UNIVERSITY

FACULTY POSITION IN BIOLOGICAL SCIENCES

The Department of Biological Sciences at Vanderbilt University seeks candidates to fill a tenure- track, assistant professor faculty position. We desire candidates whose research complements existing areas of strength within the department (**http://as.vanderbilt.edu/biosci**). The scope of the search will reflect the full breadth of the department; we are particularly interested in candidates working at the intersection of development, evolution and molecular genetics. The central criteria for the position are excellence in research and the ability to teach undergraduate and graduate students with a high level of effectiveness.

Applicants should send a single PDF containing a letter of application, *curriculum vitae*, statement of current and future research interests, and evidence of teaching effectiveness to **nikki.moore@vanderbilt.edu**. Applicants should arrange for three letters of recommendation to be sent to the same address. Review of applicants will begin **November 1, 2013**, and will continue until the position has been filled.

Vanderbilt University is an Affirmative Action/Equal Opportunity Employer. Women and under-represented minority candidates are especially encouraged to apply.

Faculty Position in Virology Department of Microbiology-Immunology Northwestern University Feinberg School of Medicine

A tenure-track position is open for a full-time faculty researcher at the level of Assistant/Associate Professor in Virology (PhD, MD/PhD or MD). Areas of particular interest include virus-cell interaction, pathogenesis, assembly, oncogenesis, immune evasion, and innate response to viral infection. Areas of study relevant to human disease are of particular interest.

All applicants should have postdoctoral research experience with substantial peer-reviewed publications that document research productivity and the ability to perform cutting edge research. A demonstrated ability to secure external funding is recommended. Candidates should have an interest in teaching graduate and medical students. Starting date and salary are negotiable. Application materials will be reviewed as received. Please send a complete CV and the name and contact information of at least three references by email to:
juniorvirologist@northwestern.edu.

Northwestern University is an Affirmative Action, Equal Opportunity Employer. Women and minorities are encouraged to apply. Hiring is contingent upon eligibility to work in the United States.

Faculty Positions in Gene Regulation and Genomics



The University of Texas Southwestern Medical Center in Dallas, the **Cecil H. and Ida Green Center for Reproductive Biology Sciences** and the Division of Basic Reproductive Biology Research in the Department of Obstetrics and Gynecology is recruiting. We invite applications from outstanding candidates for three tenure-track assistant professor positions in signaling, gene regulation, and genome function, especially in the areas of chromatin and transcription, epigenetics, nuclear endpoints of cellular signaling pathways, nuclear receptors, RNA biology, genome organization and evolution, and DNA replication and repair. We are interested in a wide variety of model systems and experimental approaches, including biochemistry, molecular biology, structural biology, animal models, genomics, proteomics, bioinformatics, and computational biology. The Green Center's research programs focus on, but are not limited to, reproduction and development in a broad sense, as well as aspects of endocrinology, stem cells, cancer, metabolism, inflammation, immunity, and neurobiology.

- ***Position 1:* Signaling, chromatin, and gene regulation** – a broad search for candidates using a wide array of experimental approaches to address fundamental questions in nuclear signaling, chromatin, transcription, epigenetics, and RNA biology.

- ***Position 2:* Genomic, bioinformatic, computational, and evolutionary approaches to understanding gene regulation** - a more focused search in areas that will connect to broader genomic initiatives on campus.

- ***Position 3:* Molecular biology of female reproductive systems** - a search for candidates using cell-based or physiological models in combination with molecular or genomic approaches to address fundamental questions concerning female reproductive biology.

The Green Center is an endowed basic science research center at UT Southwestern, which promotes and supports cutting-edge, integrative, and collaborative basic research in reproduction, development, and related areas of biology, as well as strong connections between basic and clinical research. This recruitment is part of a major university and department-supported renovation and rejuvenation of The Green Center over the past three years. Successful candidates will be housed in a newly renovated state-of-the-art research facility and provided a generous start-up package, and are expected to establish scientifically rigorous and externally funded research programs and participate in center, department, and university teaching and training programs. To learn more about The Green Center, visit: **http://www.utsouthwestern.edu/utsw/home/research/greencenter/**.

Candidates must have a Ph.D. or M.D. or equivalent in a relevant field of study, postdoctoral or comparable experience, and a demonstrated record of research excellence. Applicants should send a letter of application, curriculum vitae, and a statement of planned research projects as pdf files to **GreenCenter@UTSouthwestern.edu**, indicating the position of interest (1, 2, or 3) in the subject line. Applicants should also arrange for three letters of reference to be sent directly to the above e-mail address. Review of applications will begin on **October 15, 2013** and continue during the 2013 – 2014 academic year or until the positions are filled, although applicants are encouraged to submit their materials as soon as possible.

UT Southwestern is an Affirmative Action/Equal Opportunity Employer. Women, minorities, veterans, and individuals with disabilities are encouraged to apply.

Dartmouth

Faculty Position in Cellular and Molecular Neuroscience

The Department of Biological Sciences at **Dartmouth** seeks applicants for a tenure-track Assistant Professorship in the area of Cellular and Molecular Neuroscience. We seek candidates who are taking cellular, molecular, biophysical, genetic and/or computational approaches to address major questions in neuroscience at the cellular level including but not limited to: neuronal signaling, development and differentiation of the nervous system, or the cellular basis of neuronal degeneration. The successful candidate will be expected to direct an independent research program that will attract extramural funding, provide research training for graduate and undergraduate students, and teach at the undergraduate and graduate levels, including an undergraduate course in neuroscience. The candidate will join a larger neuroscience community at Dartmouth including faculty in the departments of Psychological and Brain Sciences, Physiology and Neurobiology, and Neurology. The department is affiliated with the Molecular and Cellular Biology graduate program and has strong collaborations with the Geisel School of Medicine at Dartmouth. Application materials should include a curriculum vitae, representative publications, statements of research and teaching interests, and at least three letters of reference. Please upload application materials electronically to: **https://secure.interfolio.com/apply/22015**

Application review will begin on **October 1, 2013** and continue until the position is filled. For further information about the department and graduate programs, see **http://dartmouth.edu/biology** as well as **http://www.dartmouth.edu/~mcb/**

One of the most diverse institutions of higher education in New England, Dartmouth College is an Equal Opportunity/Affirmative Action Employer, has a strong commitment to diversity, and in that spirit encourages applications from all individuals regardless of gender, race, religion, color, national origin, sexual orientation, age, disability, or veteran status.

University of Utah School of Medicine

Senior Faculty Position in Chemical Biology

As part of a major, institution-wide effort to develop a world-class environment for chemical biology at the University of Utah, the Department of Biochemistry is searching for an established chemical biologist for a 12-month appointment as Associate or Full Professor in the Tenure-Track. We are especially interested in investigators who are using phenotypic screens to discover new biological pathways, targets, and lead compounds, although related areas of chemical biology will also be considered. Notably strong opportunities for synergy exist in the areas of cardiovascular, cancer, metabolic, and neurological disorders. The successful candidate will have demonstrated academic excellence in original research and be committed to education. The faculty position is associated with the Center for Chemical Biology and Drug Discovery, which is part of the Utah State Technology and Research (USTAR) initiative, a long-term, state-funded investment to strengthen Utah's knowledge economy and support the commercialization of novel technologies and therapeutics. The starting date is flexible. Applications will be reviewed as they are received. The position will remain open until filled. Contact: **801-585-2555**.

Apply online at: **http://utah.peopleadmin.com/postings/26519**

The University of Utah is an Equal Opportunity/Affirmative Action Employer and educator. Minorities, women, and persons with disabilities are strongly encouraged to apply. Veterans preference. Reasonable accommodations provided. For additional information:http://www.regulations.utah.edu/humanResources/5-106.html. The University of Utah values candidates who have experience working in settings with students from diverse backgrounds, and possess a strong commitment to improving access to higher education for historically underrepresented students. The University of Utah Health Sciences Center is a patient focused center distinguished by collaboration, excellence, leadership, and Respect. The University of Utah HSC values candidates who are committed to fostering and furthering the culture of compassion, collaboration, innovation, accountability, diversity, integrity, quality, and trust that is integral to the mission of the University of Utah Health Sciences Center.

POSITIONS OPEN

UT SOUTHWESTERN MEDICAL CENTER

FACULTY POSITION in Molecular Parasitology

The Department of Pharmacology at the University of Texas (UT) Southwestern Medical Center invites applications for a tenure-track faculty position at the level of **ASSISTANT PROFESSOR** in molecular parasitology. We particularly encourage applications from those whose research focuses on the malaria parasite. The Department is strongly research-oriented with major programs in cell signaling, nuclear receptor signaling, cell cycle regulation, organelle trafficking, cancer biology, chemical biology, and parasite biology. Parasite biology is a growing interest within the department, and faculty within the department have established programs working on both protozoan and worm pathogens. Scientists within the department partici- pate in a vibrant, interdepartmental, and highly collaborative research community within the university and enjoy unparalleled access to state-of-the-art research cores in cellular imaging, protein chemistry, molecular biology, high throughput screening, animal husbandry and metabolic phenotyping, X-ray crystallography, and NMR spectroscopy.

Competitive applicants must have a relevant Ph.D. or M.D. degree, postdoctoral training, and show evidence of firm commitment to an independent research career. Outstanding candidates will be eligible for a position in the Endowed Scholars program (**website: http://www.utsouthwestern.edu/research/programs/endowed-scholars-program.html**).

Please submit curriculum vitae and a concise description of research plans (three-page limit) by October 31, 2013 to **e-mail: rxfacsearch@utsouthwestern.edu. Attention: Alfred Gilman**, Chair, Pharmacology Faculty Search Committee, UT Southwestern Medical Center. Letters of recommendation will be requested later from competitive applicants.

The University of Texas Southwestern Medical Center is an Affirmative Action/Equal Opportunity Employer. Women and minority candidates are encouraged to apply.

ASSISTANT/ASSOCIATE PROFESSOR

The College of Pharmacy, Washington State University (WSU) on the Riverpoint campus in Spokane, invites applications for a full-time, tenure-track faculty position at the rank of Assistant or Associate Professor (commensurate with experience) in the Section of Clinical Pharmacology. Applicants must have an advanced degree (M.D., PharmD., or Ph.D. in Pharmacology, Pharmaceutical Sciences, or a related discipline) before date of hire. Candidates at the level of Assistant Professor must possess a track record of accomplishment that demonstrates the potential to become an outstanding scholar and educator. Candidates considered at the rank of Associate Professor must possess a record of accomplishment demonstrating outstanding scholarly and educational activities, with a nationally recognized, extramurally funded, research program. The successful candidate is expected to maintain an active, extramurally funded research program in any relevant area (broadly defined), including pharmacology, physiology, therapeutics, and toxicology; to mentor graduate and PharmD students and fellows; and to teach in the professional and graduate curricula.

Screening of applications will begin September 15, 2013 and will continue until a suitable candidate is identified. To apply, visit **website: http://www.wsujobs.com.** Applications must include the following materials: (1) A letter of application describing your professional goals, relevant academic preparation, and experience in research and teaching; (2) Current curriculum vitae; and (3) Name, title, organization, telephone: number and e-mail address for four people willing to serve as employment references. To apply and see complete position description visit **website: http://www.wsujobs.com.**

WSU is an Equal Opportunity/Affirmative Action/ADA Educator and Employer.

POSITIONS OPEN

UT SOUTHWESTERN MEDICAL CENTER

FACULTY POSITIONS in Pharmacology

The Department of Pharmacology at the University of Texas (UT) Southwestern Medical Center invites applications for tenure-track faculty positions at the level of **ASSISTANT PROFESSOR**. The department has a long history of outstanding accomplishments in studying cellular regulatory mechanisms using a wide variety of approaches, ranging from X-ray crystallography to genetic manipulation of various organisms. We are particularly interested in strong candidates who wish to study molecular mechanisms of important biological processes either in vitro or in vivo. UT Southwestern provides a highly collaborative research community with unparalleled access to state-of-the-art core facilities and other research support.

Competitive applicants must have a relevant Ph.D. or M.D. degree and postdoctoral training, and show evidence of a firm commitment to an independent research career. Outstanding candidates will be eligible for a position in the Endowed Scholars program (**website: www.utsouthwestern.edu/research/programs/endowed-scholars-program.html**) or as a Cancer Preventive Research Institute of Texas (CPRIT) Scholar in Cancer Research (**website: http://www.cprit.state.tx.us**).

Please submit curriculum vitae and a concise description of research plans (three-page limit) by October 31, 2013 to **e-mail: rxfacsearch@utsouthwestern.edu. Attention: Alfred Gilman**, Chair, Pharmacology Faculty Search Committee, UT Southwestern Medical Center. Letters of recommendation will be requested later from competitive applicants.

The University of Texas Southwestern Medical Center is an Affirmative Action/Equal Opportunity Employer. Women and minority candidates are encouraged to apply.

ASSISTANT PROFESSOR in Inorganic Chemistry

Georgetown University wishes to recruit a tenure-track Assistant Professor in Inorganic Chemistry to begin fall 2014. Research areas in inorganic chemistry as broadly defined will be considered that complement those of existing faculty in the Department. Research interests related to clean energy, the environment, and sustainability are especially welcome. Candidates must have a Ph.D. degree in chemistry or a closely related field and postdoctoral training or equivalent is desirable. Development of an internationally recognized, externally funded research program and teaching at the undergraduate and graduate levels, are expected. Please send curriculum vitae, description of research plans, and statement of teaching philosophy as one document in PDF format, and arrange for three letters of recommendation to be sent to **e-mail: chemsearch@georgetown.edu.** For full consideration, complete applications should arrive before October 31, 2013. *Georgetown University is an Equal Opportunity/Affirmative Action Employer fully dedicated to achieving a diverse faculty and staff; applications from qualified women and minority candidates are encouraged.*

TWO FACULTY POSITIONS in Behavioral Neuroscience

The Department of Psychology at the University at Albany, State University of New York, invites applications for two tenure-track **ASSISTANT** or **ASSOCIATE PROFESSOR** positions in Behavioral Neuroscience to begin in fall 2014. Successful candidates will conduct research examining neural mechanisms of behavior and mental health using contemporary cellular, molecular, and/or genetic approaches in animal models or modern approaches to behavioral neuroscience in humans. Review of applications will begin on October 15, 2013 and continue until the position has been filled.

For further information and to apply, please visit our **website: http://albany.interviewexchange.com/jobofferdetails.jsp?JOBID=42201.**

The University at Albany is an Equal Opportunity/Affirmative Action/IRCA/ADA Employer.

POSITIONS OPEN

JOHNS HOPKINS MEDICINE

METABOLOMICS FACULTY POSITION
Biological Chemistry & Pediatrics
The Johns Hopkins University
School Of Medicine

The Departments of Biological Chemistry (BC) and Pediatrics (PD) at The Johns Hopkins University School of Medicine invite applications for a tenure-track faculty position at any rank. BC & PD are jointly seeking candidates with an outstanding record in the area of metabolomics, and a commitment to excellence in research and teaching who will conduct pioneering independent research and also serve as the faculty director of the Johns Hopkins Metabolomics Core Laboratory. Applicants should submit (preferably as a single PDF file) curriculum vitae, a list of publications, and a summary of research accomplishments and future plans by December 15, 2013. Electronic files should be sent to **e-mail: metabolomics@jhmi.edu.** Applicants should also request that three letters of recommendation be sent electronically (preferred) or mailed to the address below:

Gerald W. Hart, Ph.D.
Committee Chair
c/o Ms. Darlene Sutton
Department of Biological Chemistry
The Johns Hopkins University
School of Medicine
725 North Wolfe Street
Baltimore, MD 21205-2185

Equal Opportunity/Affirmative Action Employer.

FACULTY POSITION – VIROLOGY

The University of Texas (UT) Southwestern Medical Center, Department of Microbiology, is seeking a new faculty member in virology at the **ASSISTANT PROFESSOR** (tenure track) level. The appointee will be expected to develop a front-rank, competitive, independent research program on a medically relevant viral pathogen(s). The appointee will contribute to the teaching of medical and graduate students. An attractive startup package, including a competitive salary and generous laboratory space in a new building, is available to conduct research in a dynamic environment. Candidates also will be considered for UT Southwestern's $1.2M Endowed Scholars (startup) Program (**website: http://www.utsouthwestern.edu/education/programs/nondegree-programs/other-programs/endowed-scholars-program/index.html**). Candidates should have a Ph.D. and/or M.D. degree with at least three to four years of postdoctoral experience and an exceptional publication record. Please send a cover letter, curriculum vitae, contact information for three letters of recommendation, and a brief summary of future research to **e-mail: virologysearchcommittee@utsouthwestern.edu.**

UT Southwestern Medical Center is an Affirmative Action/Equal Opportunity Employer. Women, minorities, veterans, and individuals with disabilities are encouraged to apply.

The Campus Chemical Instrument Center NMR facility (CCIC-NMR) at the Ohio State University is seeking applicants for a **RESEARCH SCIENTIST** with a strong background in biomolecular NMR, who has strong research and collaborative skills and is expected to implement, develop, and apply state-of-the-art NMR methods for biomacromolecules and metabolomics. Review of applications will begin October 30, 2013 until the position is filled. For more information, please contact **Ms. Ruth Luketic** (**e-mail: luketic.1@osu.edu**). Applications have to be submitted through **website: https://www.jobsatosu.com/postings/search** and reference **requisition #378108.**

The Ohio State University is an Equal Opportunity/Affirmative Action Employer.

KU THE UNIVERSITY OF KANSAS

Bioinformatics/Computational Biology

The Center for Bioinformatics (Bioinformatics Program) and the Department of Molecular Biosciences invite applications for an assistant professor tenure-track faculty position to begin as early as August 18, 2014. The interdisciplinary Center for Bioinformatics (**www.bioinformatics.ku.edu**) complements existing strengths in the Department of Molecular Biosciences (**www.molecularbiosciences.ku.edu**), including structural biology, computational chemistry, proteomics, systems biology, and developmental/molecular genetics, as well as strengths in drug design and information technology in the Schools of Pharmacy and Engineering. The Center fosters international activities in Bioinformatics and combines outstanding research and a Ph.D. program.

Required Qualifications: Ph.D. and postdoctoral experience in a discipline related to Bioinformatics is expected by the start date of the appointment; potential for excellence in research in Bioinformatics; commitment to teaching life sciences courses; and strong record of research accomplishments in at least one of the following areas: modeling of macromolecular structure and interactions, modeling of protein networks, systems biology, genomics, chemical biology, and computer-aided drug discovery.

For the full position announcement and to apply online, go to: **http://employment.ku.edu** and Search Faculty Job openings, key words "Bioinformatics/Computational Biology". Submit a CV, letter of application, statement of past and future research, statement of teaching interests and philosophy, and a list of at least three references who may be contacted via telephone or e-mail. Initial review of applications begins **November 1, 2013** and will continue as long as needed to identify a qualified pool. Direct inquiries to **Dr. Ilya Vakser (vakser@ku.edu)**.

The University of Kansas is especially interested in hiring faculty members who can contribute to four key campus-wide strategic initiatives: (1) Sustaining the Planet, Powering the World; (2) Promoting Well-Being, Finding Cures; (3) Harnessing Information, Multiplying Knowledge; and (4) Building Communities, Expanding Opportunities. See www.provost.ku.edu/planning/themes/ for more information. Equal Opportunity Employer M/F/D/V.

Yale SCHOOL OF FORESTRY & ENVIRONMENTAL STUDIES

Faculty Position
Plant Physiological Ecology

The School of Forestry and Environmental Studies at Yale University invites applications for an appointment at the Full, Associate, or Assistant Professor level in Plant Physiological Ecology with a focus on woody plants. Preference will be given to applicants working at the level of whole organisms and specializing in the interaction of trees and forests with their environment.

The successful candidate will have a doctoral degree in a related field, as well as an excellent research program, grounded in plant physiology, structure, and function. Research should address problems of broad importance, such as the impacts of climate change or management practices at multiple scales, from the level of individuals and populations to large-scale ecosystems and biomes. We are especially interested in candidates with the capacity to collaborate with other faculty in a strongly interdisciplinary School, as well as with faculty in the Departments of Ecology and Evolutionary Biology, Geology and Geophysics, and Molecular, Cell and Developmental Biology.

Applicants will be expected to teach classes to PhD, Masters and undergraduate students, and to develop an internationally-recognized research program that involves graduate students, including through fieldwork. The ability to teach and conduct research in both temperate and tropical systems would be an asset.

Please submit materials by Friday, September 27, 2013 for full consideration.

To apply, visit **https://academicjobsonline.org/ajo/jobs/2686**. For questions, email fesdeansoffice@yale.edu. Salary and rank will be commensurate with experience.

Yale University is an affirmative action/equal opportunity employer; applications from women and minorities are encouraged.

http://environment.yale.edu

Tenure-Track Position in Applied Physics
Cornell University

Cornell is a community of scholars, known for intellectual rigor and engaged in deep and broad research, teaching tomorrow's thought leaders to think otherwise, care for others, and create and disseminate knowledge with a public purpose.

The School of Applied and Engineering Physics at Cornell University is seeking applications for a tenure-track, assistant professor position. Consideration of applications for an associate or full professor level position may be given to exceptionally well-qualified individuals. Candidates must be able to demonstrate the ability to develop a highly successful independent research program and to participate effectively in the teaching of the applied physics curriculum at both the undergraduate and graduate levels. Research areas of interest include biophysics and biotechnology, optics and photonics, nanostructure science and technology, novel instrumentation methods, computational physics, renewable energy, and materials physics. However, exceptional candidates in all areas of applied physics will be given serious consideration. Prospective candidates who wish to pursue interdisciplinary research efforts are strongly encouraged to apply. The successful applicant can expect a highly competitive level of support for the start-up of his/her research program. Considerable institutional resources are available at Cornell that can strengthen this research program and support interdisciplinary and collaborative research ventures. The successful candidate can expect to benefit from association with one or more of Cornell's interdisciplinary research centers, national facilities, and national resources, listed at **http://www.engineering.cornell.edu/research/facilities.cfm**. Interested applicants should go to the following link to submit their curriculum vitae, a statement of teaching philosophy, a brief (3-page limit) statement of research interests, and the names and complete contact information for at least three references: **https://academicjobsonline.org/ajo/jobs/3097**. An automated message will be sent to all references requesting letters. Applications will be accepted until December 22, 2013.

The School of Applied and Engineering Physics and the College of Engineering at Cornell embrace diversity and seek candidates who will create a climate that attracts students of all races, nationalities, and genders. Cornell University is an affirmative action/equal opportunity employer; qualified women and minority candidates are particularly encouraged to apply.

Cornell University seeks to meet the needs of dual career couples, has a Dual Career program, and is a member of the Upstate New York Higher Education Recruitment Consortium to assist with dual career searches. Visit **http://www.unyherc.org** to see positions available in higher education in the upstate New York area.

Find us online at http://hr.cornell.edu/jobs or Facebook.com/CornellCareers

Cornell University is an innovative Ivy League university and a great place to work. Our inclusive community of scholars, students and staff impart an uncommon sense of larger purpose and contribute creative ideas to further the university's mission of teaching, discovery and engagement. Located in Ithaca, NY, Cornell's far-flung global presence includes the medical college's campuses on the Upper East Side of Manhattan and in Doha, Qatar, as well as the new CornellNYC Tech campus to be built on Roosevelt Island in the heart of New York City.

Diversity and inclusion have been and continue to be a part of our heritage. Cornell University is a recognized EEO/AA employer and educator.

POSITIONS OPEN

FACULTY POSITIONS in Chemistry and Biochemistry University of California Santa Barbara

The Department of Chemistry and Biochemistry at the University of California Santa Barbara announces a search for a tenure-track faculty member for a position beginning fall 2014 at the **ASSISTANT PROFESSOR** level. Outstanding candidates with research and teaching interests in all sub-areas of inorganic chemistry, including bioinorganic, inorganic materials, and organometallic chemistry are invited to apply. In addition to contributing to the research, teaching, and service missions of the Department of Chemistry and Biochemistry, we anticipate campus-wide interactions in interdisciplinary programs between departments in the Colleges of Letters and Sciences and Engineering, along with other University-based Centers and Institutes. Applicants should submit curriculum vitae, description of their research plans, statement of graduate and undergraduate teaching interests, and arrange to have three letters of recommendation sent on their behalf to **website: https://recruit.ap.ucsb.edu/.** Review of applications will begin October 15, 2013 and will continue until the position is filled. A Ph.D. is required at the time of appointment. The department is especially interested in candidates who can contribute to the diversity and excellence of the academic community through research, teaching, and service. *The University of California is an Equal Opportunity/Affirmative Action Employer.*

TENURE-TRACK ASSISTANT/ASSOCIATE PROFESSOR

The Department of Physics at the University of Miami invites applications from highly qualified persons for a tenure–track position in Condensed Matter Physics at the Assistant or Associate Professor rank to begin fall 2014. Experimental candidates are particularly encouraged to apply. Current departmental research in this area involves electronic, magnetic, thermal, and superconductive properties of novel materials with potential device applications. Candidates must have a Ph.D. in physics or related field, a demonstrated record of research achievements, and a strong commitment to teaching and mentoring students at the undergraduate and graduate levels. The physics department is located within the University's attractive Coral Gables campus in the greater Miami area, and has a wide-ranging research expertise and established Ph.D. program. Application materials, including curriculum vitae with list of publications and statement of research plans, should be sent electronically (as a single PDF) to **e-mail: barnes@physics.miami.edu** or to: **Professor Stewart E. Barnes, CM Search Committee Chair, Department of Physics, University of Miami, Knight Physics Building, Coral Gables, FL. 33124.** Applicants should arrange for three letters of recommendation to be sent to the same address. Review of applications will begin on November 18, 2013 and continue until the position is filled. *The University of Miami is an Equal Opportunity/Affirmative Action Employer that values diversity and has progressive work-life policies. Women, persons with disabilities, and members of other underrepresented groups are encouraged to apply.*

TENURE-TRACK FACULTY POSITIONS in Bioarchaeology and Scientific Ecological Anthropology

The University of California, Santa Barbara (UCSB), Department of Anthropology, seeks a Bioarchaeologist, and a Scientific Ecological Anthropologist for tenure-track positions at the **ASSISTANT PROFESSOR** level. Submit application and materials by November 15, 2013 for the first position, and by the same date for primary consideration for the second position. For more details and to apply go to **website: https://recruit.ap.ucsb.edu.** *UCSB is an Equal Opportunity/Affirmative Action Employer.*

POSITIONS OPEN

FACULTY POSITION Chemical Biology

The Department of Biochemistry & Molecular Biology at the Drexel University College of Medicine invites applications for a tenure-track faculty position at the **ASSISTANT** or **ASSOCIATE PROFESSOR** level. We seek interactive individuals who are working at the interface of chemistry and biology, using chemical, biochemical, and/or biophysical approaches to investigate important molecular problems in biology and medicine. Individuals whose research complements existing strengths in the department are especially encouraged to apply; these strengths include protein structure/function, inhibitor/drug design, mechanistic enzymology, cell signaling, and cancer cell metabolism. The Department offers a collegial and stimulating environment with many opportunities for collaboration and state-of-the-art facilities (**website: http://www.drexelmed.edu/biochemistry**). Competitive startup funds are available. Successful candidates will have a Ph.D. and/or M.D., relevant postdoctoral experience, and a strong record of research accomplishments. Faculty are expected to establish rigorous, independent, and well-funded research programs and to participate in graduate and medical education.

The Drexel University College of Medicine is a large private medical school located in Center City Philadelphia. Drexel University is ranked among the top 100 universities in the nation, and was named as one of the top "Up-and-Coming" national universities in the 2011 U.S. News College Rankings.

To apply, please submit a single PDF containing curriculum vitae, statement of research interests, statement of teaching philosophy, and names of three references to **e-mail: lucia.boyer@drexelmed.edu;** please include the words "Chemical Biology Search" on the subject line.

ASSISTANT PROFESSOR of Biochemistry & Molecular Biology Southern Illinois University Carbondale Carbondale, IL 62901

Department of Biochemistry & Molecular Biology at Southern Illinois University (SIU) Carbondale's School of Medicine, invites applications for a tenure-track faculty position at the rank of Assistant Professor effective July 1, 2014. The successful candidate will be expected to contribute to the medical school curriculum, and research and teaching in biochemistry and molecular biology. The position includes a 100% time 12-month state-funded salary, spacious research facilities, and substantial startup funds. All applicants must have an M.D., Ph.D., or equivalent degree with experience in biomedical research including cancer. At least two years of postdoctoral experience is required. This is a security sensitive position. Before any offer of employment is made, the university will conduct a pre-employment investigation, which includes a criminal background check. Additional departmental and job information can be obtained via the following **website: http://www.siu.edu/jobs.** Review of the applications will begin February 1, 2014 and will continue until the position is filled. Applicants shall submit curriculum vitae, description of research and teaching interests, and arrange to have at least three reference letters sent to: **Ramesh Gupta, Chair, Biochemistry & Molecular Biology, School of Medicine, Mail Code 4413, Southern Illinois University Carbondale, 1245 Lincoln Drive, Carbondale, IL 62901,** or **e-mail: bmbsearch@siumed.edu.**

SIU Carbondale is an Affirmative Action/Equal Opportunity Employer that strives to enhance its ability to develop a diverse faculty and staff and to increase its potential to serve a diverse student population. All applications are welcomed and encouraged and will receive consideration.

POSITIONS OPEN

FACULTY POSITIONS IN NEUROSCIENCE

As part of the 2nd Century Initiative (**website: http://secondcentury.gsu.edu**) at Georgia State University (GSU) the Neuroscience Institute (**website: http://neuroscience.gsu.edu**) together with the Departments of Biology (**website: http://biology.gsu.edu**) and Psychology (**website: http://www2.gsu.edu/~wwwpsy**), is seeking to hire up to two faculty members to complement GSU's current strengths in systems, behavioral, and computational neuroscience and extend them into the areas of Neurogenomics and the Molecular Basis of Behavior. Research using invertebrates or aquatic and amphibian vertebrates is especially desired but research in any area of neurogenomics and molecular neuroscience is appropriate. We are seeking individuals at the **ASSOCIATE** or **FULL PROFESSOR** level, although junior candidates will be considered if they are tenure-eligible. Candidates are expected to have a strong research program including external funding.

Applications should include a full curriculum vitae, names and contact information for three references, and a letter of research interests. Applications can be submitted either electronically in PDF format to the search committee chair, **Dr. Paul S. Katz** (**e-mail: pkatz@gsu.edu**) or in hard copy to: **Chair of the Neurogenomics Search, Neuroscience Institute, Georgia State University, PO Box 5030, Atlanta, GA 30302.**

Review of applications will begin immediately and will continue until the positions are filled.

Georgia State University, a Research University of the University System of Georgia, is an Affirmative Action/Equal Employment Opportunity Employer.

ASSISTANT PROFESSOR in Population Ecology

Department of Fish and Wildlife Sciences, University of Idaho, seeks an Assistant Professor in Animal Population Ecology and Modeling. Position will be 30%–35% teaching, 45%–60% scholarship, and 10%–25% advising/outreach/service. Incumbent will develop an extramurally funded research program addressing ecological and management-relevant questions related to ecology/dynamics of wild animal populations. Courses include senior-level population ecology, graduate course in population analysis, and graduate course or seminar in area of specialty. Requirements include expertise in population ecology and modeling with emphasis on impacts of anthropogenic and natural influences on wildlife populations; knowledge of processes affecting wildlife populations; demonstrated research productivity through external funding and publications; and commitment to teaching excellence. Review of applications will begin on 1 October 2013. Starting date August 2014. For a complete description and to apply online visit **website: https://www.sites.uidaho.edu/AppTrack/Agency/Applicant/ViewAnnouncement.asp?announcement_no=10000051846.** Contact **Dr. Courtney Conway** with questions at **telephone: 208-885-6176.**

FACULTY POSITION Basic Research in Infectious Diseases

The Division of Infectious Diseases of Boston Children's Hospital announces a search for a new M.D. or Ph.D. faculty member to establish an independent research program focused on microbial pathogenesis or host immune response. The successful applicant will hold a faculty appointment at Harvard Medical School. Outstanding facilities and ample opportunities for collaboration are available within the division (**website: http://www.childrenshospital.org/id**) and in the Harvard biomedical community. Please respond with a description of research and goals, curriculum vitae, and contact information for three references to Infectious Diseases Search Committee c/o **Ms. Nora Boyle, e-mail: nora.boyle@childrens.harvard.edu.** *Boston Children's Hospital is an Equal Opportunity Employer; women and minority candidates are encouraged to apply.*

Stanford | ENGINEERING
Mechanical Engineering

Stanford University
Department of Mechanical Engineering
Faculty Opening

Stanford University's Department of Mechanical Engineering invites applications for tenure-track faculty positions in product design, at all levels. We are primarily interested in applicants who will perform design research and teach design classes at the intersections of technology, business, and behavioral science. We seek candidates, preferably with an earned doctorate, who will conduct creative and independent research programs with a deep understanding of design. An ideal candidate would be an accomplished designer with a background in the conception and creation of products, and would demonstrate the potential to build an exemplary program of research. Successful candidates should also be strategic thinkers and contribute to the advancement and development of design as a discipline at Stanford.

The Department of Mechanical Engineering offers an appealing and collegial setting for faculty and students studying design. The undergraduate Product Design major is among the most popular in the School of Engineering. There is also a unique two-year Master's program. Teaching is interactive and project-based, and is supported by an extensive Product Realization Laboratory and Studio. We encourage collaboration with faculty members in Mechanical Engineering, as well as other departments and disciplines across the university. Formal connections with other departments will also be considered. The Design Group is actively affiliated with the Hasso Plattner Institute of Design at Stanford (known as the d.school), and participates in research in other programs within Stanford at the intersection of technology, business and behavioral sciences, including the Center for Design Research, the Stanford Learning Lab, the Center for Work, Technology and Organization, the Human/Computer Interaction Group in the Computer Science Department, and the Learning Design and Technology Program in the School of Education.

Applicants should submit a cover letter, a curriculum vitae with a list of publications, a one-page statement each of research vision and teaching interests, a brief (~4 page) portfolio of original design work, and the names and email addresses of five references. Please submit your application online at:
http://me.stanford.edu/research/open_positions.html

The review of applications will begin on **October 1, 2013**. However, applications will be accepted until the position is filled.

Stanford University is an Equal Opportunity Employer and is committed to increasing the diversity of its faculty. It welcomes nominations of and applications from women and members of minority groups, as well as others who would bring additional dimensions to the university's research and teaching missions.

UT SOUTHWESTERN MEDICAL CENTER

Assistant Professor of Biochemistry

The Department of Biochemistry at The University of Texas Southwestern Medical Center invites applications from candidates for a tenure-track faculty position at the rank of Assistant Professor. Candidates should be engaged in innovative research within the broad fields of biochemistry or molecular biology. UT Southwestern maintains state-of-the-art facilities and employs a faculty that includes five Nobel Laureates and nineteen members of the National Academy of Sciences. The Biochemistry Department offers a vibrant environment for research, generous start-up support, and participation in graduate-level teaching. Applicants should submit a *curriculum vitae*, a concise description of research plans, and three letters of reference by **November 1, 2013** to the attention of Dr. Steven L. McKnight, Chair, Department of Biochemistry at **Biochem.Search@UTSouthwestern.edu**.

UT Southwestern Medical Center is an Affirmative Action/Equal Opportunity Employer. Women, minorities, veterans and individuals with disabilities are encouraged to apply.

NORTHWESTERN UNIVERSITY

The Department of Physiology (**http://www.physio.northwestern.edu**) of the Northwestern University Feinberg School of Medicine in downtown Chicago invites applications for a full time tenure track position at the Assistant - Full Professor rank in the area of cellular and/or systems neuroscience.

Applicants should have a Ph.D. or M.D. degree and an outstanding record of research in cellular and/or systems neuroscience that adds to existing departmental strengths in sensorimotor integration, pain perception, studies of neurodegeneration, and learning and memory. Individuals using animal models and innovative experimental techniques including biochemical or molecular approaches, optical imaging, optogenetics, multi-electrode recordings and behavioral measures are particularly encouraged to apply, but the scientific excellence of the candidate is more important than the particular area of research.

Applicants should send (as a single PDF) a cover letter, curriculum vitae, a two-page description of research accomplishments and plans, and the name and contact information for three references to **cellular-systems-neuroscience@northwestern.edu**. *Please quote reference number 21007.* Start date is negotiable.

Northwestern University is an Affirmative Action, Equal Opportunity Employer. Women and minorities are encouraged to apply. Hiring is contingent upon eligibility to work in the United States.

CALIFORNIA INSTITUTE OF TECHNOLOGY invites applications for a tenure-track faculty position at the assistant professor level in the Division of Chemistry and Chemical Engineering in the following areas:

Inorganic Chemistry

Candidates with strong commitments to research and teaching excellence are encouraged to apply. The term of the initial appointment is four years, and the appointment is contingent upon completion of all requirements for a Ph.D. in chemistry or in a related field. Submit curriculum vitae, publication list, a description of proposed research, and three letters of recommendation via e-mail to Chair of the Inorganic Search Committee: **inorg@caltech.edu**. Applications should be received by **October 15, 2013**.

Organic Chemistry, with an emphasis on chemical biology and organic materials

Candidates with strong commitments to research and teaching excellence are encouraged to apply. The term of the initial appointment is four years, and the appointment is contingent upon completion of all requirements for a Ph.D. in chemistry or in a related field. Submit curriculum vitae, publication list, a description of proposed research, and three letters of recommendation via e-mail to Chair of the Organic Search Committee: **chembiol@caltech.edu**. Applications should be received by **October 15, 2013**.

Theoretical and Experimental Physical Chemistry

Candidates with strong commitments to research and teaching excellence are encouraged to apply. The term of the initial appointment is four years, and the appointment is contingent upon completion of all requirements for a Ph.D. in chemistry or in a related field. Submit curriculum vitae, publication list, a description of proposed research, and three letters of recommendation via e-mail to Chair of the Physical Chemistry Search Committee: **chemphys@caltech.edu**. Applications should be received by **October 15, 2013**.

For more information please visit:
https://applications.caltech.edu

The California Institute of Technology is an Equal Opportunity/Affirmative Action Employer. Women, minorities, veterans, and disabled persons are encouraged to apply.

POSITIONS OPEN

FACULTY POSITIONS in Cancer Research
University of Notre Dame

As part of a campus-wide initiative associated with the Harper Cancer Research Institute (**website: http://HarperCancer.nd.edu/**), multiple open-rank tenure-track faculty positions are available at the University of Notre Dame in the broad area of cancer research. Individuals engaged in basic and translational cancer research using organotypic and/or animal models of cancer are especially encouraged to apply. A demonstrated record of collaborative and interdisciplinary research is strongly preferred. Successful candidates will be appointed in either the Department of Biological Sciences or the Department of Chemistry and Biochemistry and will be expected to establish a vigorous extramurally supported research program in cancer biology/biochemistry, participate in collaborations within and across disciplines, and contribute to excellence in undergraduate and graduate education. Senior applicants should have a record of national and international distinction. Key research facilities include the AAALAC-accredited Freimann Animal Facility, Notre Dame Integrated Imaging Facility, Center for Zebrafish Research, Eck Institute for Global Health, Keck Center for Transgene Research, Center for Rare and Neglected Diseases, Lizzadro Magnetic Resonance Research Center, Center for Research Computing, and core facilities for proteomics, genomics and bioinformatics. Additional information can be found at **website: http://research.nd.edu/core-facilities/.** The Harper Cancer Research Institute represents a collaboration between the University of Notre Dame and Indiana University School of Medicine-South Bend (**website: http://medicine.iu.edu/southbend**) and is housed in 55,000 square feet of new research space. The University is also engaged in the Indiana Clinical and Translational Sciences Institute (I-CTSI) partnership with Indiana University School of Medicine (Indianapolis) and Purdue University. The positions include competitive salary, startup funding, and laboratory space. Applicants should upload a cover letter, curriculum vitae, detailed research plan, and statement of teaching interests directed to **M. Sharon Stack**, Director of the Harper Cancer Research Institute (**website: https://academicjobsonline.org/ajo/jobs/2962**). Candidates must also arrange to have at least three letters of recommendation sent directly to the search committee via the application website, although senior applicants can apply in confidence. Review of applications will commence immediately and will continue until suitable candidates are identified.

The University of Notre Dame is an Equal Opportunity Employer with a strong institutional and academic commitment to diversity and endeavors to foster a vibrant learning community animated by the Catholic intellectual tradition.

FACULTY POSITION in
Evolutionary Biology

The Department of Zoology, University of Wisconsin-Madison, invites applications for a tenure-track position at the **ASSISTANT PROFESSOR** level, beginning August 2014. Requirements include a Ph.D and postdoctoral experience in evolutionary biology or related area and demonstrated research accomplishments. Teaching will include courses at the undergraduate and graduate level.

For additional information, see our departmental **website: http://www.wisc.edu/zoology.** Please send a single PDF file containing your cover letter, complete curriculum vitae, statement of research and teaching interests, and full contact information for three references to the Evolutionary Search Committee to **e-mail: evolutionarybio@zoology.wisc.edu.**

Questions should be directed to: Evolutionary Biology Search Committee at **e-mail: evolutionarybio@zoology.wisc.edu,** or **fax: 608-262-9083.** Deadline: For full consideration, apply by December 1, 2013. Only applications submitted by e-mail will be accepted.

An Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply. A criminal background check will be required prior to appointment. Unless confidentiality is requested in writing information regarding applicants must be released upon request. Finalists cannot be guaranteed confidentiality.

POSITIONS OPEN

PHYSICAL CHEMISTRY FACULTY POSITION
University of Oregon

The Department of Chemistry & Biochemistry (**website: http://chemistry.uoregon.edu**) invites applications for a tenure-related position in experimental physical chemistry (broadly defined) beginning fall 2014 at the anticipated rank of **ASSISTANT PROFESSOR.** A Ph.D. is required and postdoctoral experience is preferred. The potential for establishing a vigorous independent research program in physical chemistry and active participation and excellence in teaching at the undergraduate and graduate levels will be the most important criteria for selection. In addition to membership in the Department of Chemistry & Biochemistry, the successful candidate will have the opportunity to pursue research in a variety of interdisciplinary institutes (see **website: http://chemistry.uoregon.edu/research.html?institutes**). To ensure consideration, please submit application materials by October 25, 2013 at **website: https://academicjobsonline.org/ajo/jobs/3135** and upload curriculum vitae, a statement of research plans and objectives, and a brief statement of teaching philosophy or interests. The candidate should also arrange for three letters of recommendation to be submitted directly by the recommenders via the preceding URL link. The position will remain open until filled. *The University of Oregon is committed to creating a more inclusive and diverse institution and seeks candidates with demonstrated potential to contribute positively to its diverse community. The University of Oregon is an Equal Opportunity/Affirmative Action/ADA Institution committed to cultural diversity.*

ASSISTANT PROFESSOR in
Macroevolutionary Biology
Iowa State University

The department of Ecology, Evolution & Organismal Biology (EEOB) at Iowa State University invites applications for a tenure-track position at the Assistant Professor level in Macroevolutionary Biology. We seek a creative individual employing and/or developing macroevolutionary and phylogenetic comparative approaches to address key questions in the evolution of organismal systems and biological diversity. Successful candidates will join a dynamic department embedded in a highly integrative and collaborative campus. Applicants must have a Ph.D., are expected to establish a nationally recognized, externally funded research program, and will contribute skillfully to undergraduate and graduate education. For a full description of the position, see **website: http://www.eeob.iastate.edu/search.html.**

Application instructions are at **website: http://www.iastatejobs.com** (**vacancy #131002**). Applicants should submit a cover letter, curriculum vitae, research/vision statement that includes how their research program addresses unresolved problems in the field, a teaching statement, and up to three reprints by 15 October 2013. Submission of three confidential letters of recommendation should be arranged as per instructions in the online application system.

Iowa State University values diversity and is an Affirmative Action/Equal Employment Opportunity Employer with an NSF ADVANCE program.

ASSISTANT PROFESSORSHIP in
Genetics
Western Washington University

The Biology Department at Western Washington University (WWU), a regional comprehensive university located between Seattle and Vancouver B.C., invites applications for a tenure-track, assistant professor position, beginning September 2014. We seek an individual committed to undergraduate and M.S. education who will establish a vigorous research program that involves students. Ph.D. and postdoctoral experience in genetics using quantitative or statistical methods are required. The applicant must provide evidence of the ability to teach genetics and biostatistics. Review begins October 21, 2013. See full position announcement, including all required and preferred qualifications, at **website: http://biol.wwu.edu/biology/.** For application information and instructions, go to the WWU Employment **website: http://www.wwu.edu/jobs.** *Affirmative Action/Equal Opportunity Employer.*

POSITIONS OPEN

TENURE-TRACK FACULTY POSITION IN RESPIRATORY AND INFECTIOUS DISEASES. Center for Veterinary Health Sciences, Oklahoma State University (OSU) invites applications for a tenure-track position at the rank of **ASSISTANT/ASSOCIATE PROFESSOR** as part of the NIH-funded Centers for Biomedical Research Excellence (CoBRE), Oklahoma Center for Respiratory and Infectious Diseases. A Ph.D., D.V.M., or equivalent degree in a relevant field is required. The candidates who have a research focus on influenza virus or RSV with current research funding are particularly desirable although candidates with background in other respiratory infectious diseases will be considered. The successful candidate will be expected to develop and maintain an extramurally supported research program, collaborate with center investigators, participate in center activities, and contribute to graduate education. Stillwater is a growing college town (population about 50,000) with a low cost of living located about one hour from both the Oklahoma City and Tulsa metropolitan areas. Interested individuals should submit an application in a single PDF file including cover letter, curriculum vitae, brief statement of research interests and goals, and the names of three references to: **Dr. Lin Liu, CoBRE Director and Chair of the Search Committee, 264 McElroy Hall, Center for Veterinary Health Sciences, Oklahoma State University, Stillwater, OK, 74078** (**e-mail: lin.liu@okstate.edu**). For full consideration, applications should be received by November 15, 2013. Review of applications will continue until suitable candidates are identified. *OSU is an Equal Opportunity/Affirmative Action Employer that encourages applications from members of minority groups.*

FACULTY POSITION in
Molecular, Cellular, and Developmental Biology
University of Colorado Boulder

The Department of MCD Biology invites applications for a tenure-track **ASSOCIATE** or **FULL PROFESSOR** in the area of genetics, molecular, cellular, or developmental biology broadly defined. Applicants must have a Ph.D., M.D., or equivalent, and an excellent track record of external funding and research productivity. The candidate is expected to maintain his/her vigorous and innovative research program, and have enthusiasm for teaching at the undergraduate and graduate levels. The successful candidate will forge an area of research new to MCDB or broaden our existing strengths.

Review of applications will begin on 1 November 2013 and continue until the position is filled. Application materials are accepted electronically at **website: https://www.jobsatcu.com, posting number F00664.** Applicants should submit curriculum vitae, a concise statement of research and teaching interests, and a list of three references.

For questions or concerns on submitting your materials electronically, please contact **e-mail: mcdbsrch@colorado.edu.**

The University of Colorado is an Equal Opportunity Employer.

FACULTY POSITION in
Inorganic Chemistry at the
University of California, Irvine

The Department of Chemistry at the University of California (UC), Irvine invites applications from outstanding individuals for a tenure-track position at the **ASSISTANT PROFESSOR** level in the field of Inorganic Chemistry. Candidates must have a Ph.D. in Chemistry or a related field; postdoctoral experience is desirable. The position requires both the establishment of a vigorous research program and a strong commitment to teaching at undergraduate and graduate levels. Applications must be submitted electronically via the Internet at **website: https://recruit.ap.uci.edu/apply/JPF02110.** Applicants should upload a cover letter, curriculum vita (including publication list), and a concise statement of proposed research. At least three letters of recommendation will be required. Applications and supporting materials should be received by October 15, 2013 for full consideration. *The University of California, Irvine is an Equal Opportunity/Affirmative Action Employer committed to excellence through diversity. UC Irvine has an active ADVANCE Gender Equity Program.*

Faculty Positions Available in the Department of Cell and Molecular Biology Feinberg School of Medicine, Northwestern University

The Department of Cell and Molecular Biology at the Feinberg School of Medicine, Northwestern University, seeks to recruit several full-time tenure-track faculty working in the fields of cell and molecular biology. Positions are available at all ranks from assistant to full professor. Applicants must hold a PhD or MD/PhD degree. Applications, including a cover letter, a curriculum vitae and a statement of research interests should be sent electronically as a single pdf document to **cmbsearch@northwestern.edu**.

Candidates applying for an Assistant Professor position should provide three letters of recommendation which must be submitted electronically to the same e-mail address. Letters should be provided in pdf format and should include the name of the applicant in the subject line. Candidates for Associate or Full Professor should provide names and the contact information of three individuals willing to submit letters of recommendation on their behalf.

Northwestern University is an Affirmative Action/Equal Opportunity Employer. Hiring is contingent upon eligibility to work in the United States. Women and minorities are encouraged to apply.

FACULTY APPOINTMENT IN CELL BIOLOGY Department of Cell Biology Duke University Medical Center

The Department of Cell Biology at Duke University Medical Center is hiring a tenure-track faculty member. The preferred level is for an Assistant Professor who would start his/her independent career at Duke. Candidates with demonstrated success in addressing important and fundamental questions of developmental, regenerative, or cellular biology are encouraged to apply. Preference will be given to candidates whose activities complement and strengthen research programs within the department (**http://www.cellbio.duke.edu/**). Successful candidates will have track records of creativity and productivity, demonstrated potential for outstanding future achievements, and a desire to participate in an exciting, interactive, and growing community. They will be expected to mount a productive and innovative research program, to obtain outside funding, and to participate actively in graduate training. Candidates must have a Ph.D., M.D. or equivalent degree. Minority candidates are especially encouraged to apply. For full consideration, applications should be submitted by **November 15, 2013**, although applications will be considered until the position is filled. Applicants should submit curriculum vitae, a brief summary of current and proposed research, and 3 letters of recommendation to **https://academicjobsonline.org/ajo/jobs/3082**.

Questions may be directed to the Search Committee Chair, Ken Poss, Department of Cell Biology (**cellbiofacultysearch@dm.duke.edu**)

Duke University is an Equal Opportunity Affirmative Action Employer.

SANFORD HEALTH

TRANSLATIONAL FACULTY POSITIONS SANFORD CHILDREN'S HEALTH RESEARCH CENTER SANFORD RESEARCH/USD

The Sanford Children's Health Research Center (CHRC, Sioux Falls, SD **http://www.sanfordresearch.org/researchcenters/childrenshealth/**), invites applications from scientists and physician-scientists for full time junior or senior faculty positions within Sanford Research/USD (**http://www.sanfordresearch.org**) with commensurate rank of Assistant Professor, Associate Professor, or Professor in the Departments of Pediatrics and Neurosciences of the Sanford School of Medicine at The University of South Dakota. An historic $400 million gift by philanthropist Denny Sanford has allowed for expansion of Sanford Research/USD and development of the CHRC, a center specifically focusing on children's health research.

We seek outstanding scientists with research programs that contribute to one of the following areas; contribute to the understanding of developmental programming of diseases or contributing to the molecular understanding and treatment of childhood neurological diseases. For MD applicants, board certification or eligibility in a pediatric subspecialty or neurology is highly desirable.

Applicants should hold an MD and/or PhD degree (or equivalent). Successful applicants will complement existing strengths within the CHRC, which includes expertise in in lipid mediated developmental programming in offspring of diabetic or obese mothers, cortical development, autophagy, axonal polarity, bioenergetics, neurodegeneration, neuronal migration disorders, neurogenetics, and animal models of disease. Junior candidates will be expected to develop independent research programs with extramural funding. Senior candidates should have a demonstrated track record of extramural grant support and publications and be capable of providing mentorship to junior faculty members within the CHRC while advancing their independent research programs. Researchers will join the energetic interdisciplinary and collaborative and collegial research community at Sanford Research/USD and hold both Sanford Research/USD and Sanford School of Medicine faculty appointments. Successful MD applicants will be assigned clinical duties within the Division of Pediatrics at the Sanford Children's Hospital. (**http://www.sanfordhealth.org/Locations/MedicalCenters/SanfordChildrensHospital/siouxfalls**)

Significant institutional support, including modern laboratory space and state-of-the-art facilities, will be provided in the Sanford Center. A well-developed laboratory core system is provided to facilitate new research efforts. In addition, a comprehensive compensation package will be tailored to the individual's qualifications. Sanford Health is an Equal Opportunity/Affirmative Action Employer. Candidates should submit a single PDF including a detailed curriculum vitae and a description of research experience and future plans that includes relevance to children's research. Candidates should also submit at least three letters of recommendation. All application materials should be sent by email to: **David A Pearce Ph.D., Director, Children's Health Research Center, Sanford Research/USD, Professor, Department of Pediatrics, Sanford School of Medicine of The University of South Dakota, 2301 E. 60th Street North, Sioux Falls, SD 57104; Telephone: 605-312-6004; FAX: 605-312-6071; Email: David.Pearce@sanfordhealth.org.**

University of Massachusetts UMASS Medical School

RNA Therapeutics Institute Tenure-Track Positions

The RNA Therapeutics Institute (RTI) at the University of Massachusetts Medical School, co-directed by Victor Ambros, Craig C. Mello, Melissa J. Moore, and Phillip D. Zamore, invites applications for tenure-track faculty positions. Successful candidates will conduct innovative research to understand normal physiology and development, disease mechanisms and/or will develop novel diagnostics or therapies. Candidates need not necessarily conduct research directly focused on RNA biology or therapeutics development, but should indicate how their research will synergize with ongoing research within the RTI and the greater UMass Medical School community.

Research areas of interest include, but are not limited to: (1) genetics and biochemistry in model organisms, (2) human genetics and pathophysiology (3) structural biology, (4) chemical biology; (5) engineering of nucleic acids for controlled therapeutic delivery and optimal efficacy *in vivo*. **Physician scientists, synthetic chemists, materials scientists, computational researchers, bioengineers, geneticists, cell** and **molecular biologists**, and **biochemists** are all encouraged to apply. Also desired are scientists with significant industrial experience who wish to return to academia.

The RTI is housed in a new state-of-the-art research building, and is central to a campus-wide interdisciplinary initiative in RNA therapeutics, stem cell biology and gene therapy designed to facilitate collaboration among basic scientists, preclinical investigators and clinicians. As a recipient of a Clinical and Translational Science Award (CTSA) from the NIH, UMass Medical School seeks to build an environment in which basic, applied and clinical researchers collaborate to inform our understanding of human disease and accelerate development of novel diagnostics and therapies. To further encourage collaboration, all RTI investigators hold joint appointments within other departments on campus.

Applicants should submit a cover letter, curriculum vitae, a two-page statement of research interests, and contact information for three references to **https://academicjobsonline.org/ajo/jobs/3077**. Applications will be reviewed expeditiously, with interviews commencing in October. Multiple positions are available and will remain open until filled. Inquiries (but not application materials) may be directed to Darla Cavanaugh at **darla.cavanaugh@umassmed.edu**. Applications at the Assistant, Associate and Full Professor levels will be considered.

As an Equal Opportunity and Affirmative Action Employer, UMMS recognizes the power of a diverse community and encourages applications from individuals with varied experiences, perspectives and backgrounds.

POSITIONS OPEN

YALE UNIVERSITY
Energy Sciences Institute

Yale University seeks to recruit faculty at the **ASSISTANT PROFESSOR** level to the newly established Energy Sciences Institute. The Institute is one of several science and engineering initiatives located at Yale's West Campus, a recently acquired 137-acre campus that has provided the University with unparalleled opportunities to stimulate and support cutting-edge, interdisciplinary research. We seek creative teacher-scholars who will have a primary appointment in the Chemistry Department. Candidates must have a Ph.D. in a relevant discipline, and an outstanding record of research that demonstrates originality in addressing significant questions in the study of energy. The Search Committee is particularly interested in individuals with expertise and research interests in the conversion of solar energy into storable chemical energy. Applicants should create a profile at **website: https://academicjobsonline.org/ajo/jobs/2996** and upload a statement of research plans, curriculum vitae, and up to five reprints of published work(s). Applicants should also arrange for three references to upload their letters of recommendation. For further information, contact: **Ryan Croteau** at **e-mail: ryan.croteau@yale.edu** or **P.O. Box 27394 West Haven, CT 06516-7390.** The review of applications will begin on October 15, 2013.

Yale University is an Affirmative Action/Equal Opportunity Employer. Yale values diversity among its faculty, students, and staff and strongly encourages applications from women and underrepresented minorities.

ASSISTANT PROFESSOR of Neuroscience

The School of Biological Sciences at Illinois State University in Normal, Illinois, (**website: http://www.bio.illinoisstate.edu**) invites applications for a nine-month tenure-track position in **MOLECULAR NEUROSCIENCE** at the level of Assistant Professor to begin August 16, 2014. The ideal candidate will address cutting-edge neuroscience at the molecular level. Preferred areas of research expertise include but are not limited to RNA-mediated regulation, nucleotide-repeat or methylation pathologies, epigenetics, or transcriptomics. Establishment of a competitive extramurally funded research program is expected. The new faculty member will participate in new undergraduate and graduate degree tracks related to neuroscience and molecular biology, with primary teaching responsibilities in these two disciplines, and mentor B.S., M.S., and Ph.D. students. Postdoctoral experience required. Please complete an online application for **posting number 0705515** at **website: http://www.IllinoisState.edu/jobs** and additionally send cover letter, curriculum vitae, a brief statement of research goals, and contact information for three references as a single PDF file to **Dr. Paul A. Garris,** Molecular Neuroscience Search Committee, **in c/o Sally Little** via **e-mail: salitt2@ilstu.edu.** Review of applications will begin on September 30, 2013 and continue until position is filled.

Illinois State University is an Equal Opportunity University encouraging diversity.

INDIANA UNIVERSITY, BLOOMINGTON
Experimental Inorganic Chemistry

The Department of Chemistry at Indiana University invites applications for a **SENIOR FACULTY POSITION** in experimental inorganic chemistry, broadly defined, beginning August 2014. A Ph.D. in inorganic chemistry or a related field is required. Successful candidates will be expected to possess a visible, externally funded research program and teach at the graduate and undergraduate levels. Candidates should send a complete curriculum vitae and summary of future research plans to: **Chair, Inorganic Faculty Search Committee, Department of Chemistry, Indiana University, 800 E. Kirkwood Avenue, Bloomington, IN 47405** and PDF files electronically to **e-mail: chemchair@indiana.edu.** Applications completed by October 15, 2013 will receive full consideration, but review will continue until the position is filled.

Indiana University is an Affirmative Action/Equal Opportunity Employer and especially encourages applications from women and members of minority groups.

POSITIONS OPEN

YALE UNIVERSITY
Chemical Biology Institute

The Chemical Biology Institute, a cornerstone of Yale's new West Campus research enterprise, invites applications for tenure-track positions at the **ASSISTANT PROFESSOR** level to commence 1 July 2014. Faculty associated with the Chemical Biology Institute will hold primary appointments in any of several life science or physical science departments within the Faculty of Arts and Sciences, the School of Engineering and Applied Science, or the Yale School of Medicine. At this time, we seek to identify two (2) candidates whose research interests and accomplishments align best with the Institute and either the Department of Chemistry (**website: http://www.chem.yale.edu/**) or the Department of Molecular, Cellular, and Developmental Biology (**website: http://mcdb.yale.edu**). Successful candidates will be creative teacher-scholars with reputations for outstanding research at the combined interface of chemistry, biology, and/or medicine, and must possess a Ph.D. in a relevant discipline. Applicants should create a profile at **website: https://academicjobsonline.org/ajo/jobs/2993** and upload a statement of research plans, curriculum vitae, and up to five reprints of published work(s). Applicants should also arrange for three references to upload their letters of recommendation, and identify in their cover letter the department that best aligns with their research interests and training. For further information, contact: **Paula Maher-Rivera** at **e-mail: paula.maher@yale.edu** or **PO Box 27392, West Haven, CT 06516-7392.** The review of applications will begin on 15 October 2013. *Yale University is an Affirmative Action/Equal Opportunity Employer. Yale values diversity among its faculty, students, and staff and strongly encourages applications from women and underrepresented minorities.*

TENURE-TRACK ASSISTANT PROFESSOR
Indiana University, Bloomington Chemical Biology or Bioorganic Chemistry

The Department of Chemistry at Indiana University invites applications for a tenure-track faculty position at the assistant professor level in chemical biology or bioorganic chemistry beginning August 2014. The search is open to all areas of chemical biology and bioorganic chemistry, as broadly defined, including areas such as macromolecule synthesis, bioactive polymer synthesis, metabolic profiling, glycobiology, and synthetic biology. A Ph.D. in chemistry, or a related field, and postdoctoral experience are required. Successful candidates will be expected to develop a visible, externally funded research program. Primary teaching assignments will include graduate courses in chemical biology and undergraduate biochemistry. The candidate will participate in a new graduate training program in Quantitative and Chemical Biology at Indiana University (**website: http://www.chem.indiana.edu/qcb/**). Applicants should send complete curriculum vitae, a summary of future research plans, and arrange to have four letters of recommendation forwarded to the department. Applications completed by October 15, 2013 will receive full consideration, but review will continue until the position is filled. Applications and recommendation letters should be addressed to: **Professor Michael S. VanNieuwenhze, Chair, Faculty Search Committee, Department of Chemistry, Indiana University, 800 E. Kirkwood Avenue, Bloomington, IN 47405** and sent as PDF files electronically to **e-mail: chemchair@indiana.edu.**

Indiana University is an Affirmative Action/Equal Opportunity Employer and especially encourages applications from women and members of minority groups.

Help employers find you.
Post your resume/cv.
www.ScienceCareers.org

POSITIONS OPEN

OPEN CHEMISTRY FACULTY POSITION
Wayne State University

The Department of Chemistry at Wayne State University seeks applications for a tenure-track or tenured faculty position in any area of chemistry, including analytical, biological, chemical biology, inorganic, materials, organic, physical, and theoretical, with an anticipated starting date of August 2014. Candidates should have a Ph.D. degree in chemistry or related discipline and a strong commitment to excellence in both undergraduate and graduate education. Junior candidates are expected to develop a nationally recognized, externally funded research program and should send an application letter, curriculum vitae, a description of future research plans and broader impacts thereof, a statement of teaching philosophy, and three letters of recommendation. Mid-career and senior candidates should have an established record of excellence in teaching and research and should send an application letter and curriculum vitae. The Department of Chemistry offers a competitive startup package and an outstanding environment for research in newly renovated research laboratories. The fully staffed Lumigen Instrument Center in the Chemistry Department manages state-of-the-art high field NMR spectrometers, mass spectrometers, single crystal and powder X-ray diffractometers, SEM and TEM, and EPR instrumentation. More information about the Department can be found at **website: http://www.chem.wayne.edu.** All materials should be sent to: **Professor Charles H. Winter, Associate Chair, 153 Chemistry, Wayne State University, 5101 Cass Avenue, Detroit, Michigan 48202-3489.** Review of applications will begin in October 2013. *Wayne State University is an Equal Opportunity/Affirmative Action Employer. Women and minority candidates are encouraged to apply.*

TWO OPEN FACULTY POSITIONS
Boston College
Chemistry Department

The Chemistry Department of Boston College invites applications for two tenure-track positions to be effective in the fall of 2014. Applicants will be evaluated based on their potential to establish a prominent and well-funded research program and to excel in teaching at the graduate and undergraduate levels. Successful applicants will join a department of approximately 120 doctoral students, 30 postdoctoral fellows, 200 undergraduate majors, and an internationally recognized faculty.

ASSISTANT PROFESSORS in the (broadly defined) areas of Organic Chemistry and Experimental Physical/Materials Chemistry: requires a Ph.D. in Chemistry or related areas; postdoctoral experience is desirable but not required. The candidate is expected to have published in top refereed journals and demonstrated the ability to perform outstanding independent research.

Interested applicants must submit a cover letter, a graphical executive summary of research plans (one page), curriculum vitae, a summary of research plans (eight pages maximum), a statement of teaching philosophy and arrange to have three letters of reference submitted via the online faculty application at **websites: https://secure.interfolio.com/apply/21985** for physical/materials chemistry and **https://secure.interfolio.com/apply/21965** for organic chemistry. In the cover letter, the names of three references should be specified.

All application materials must be submitted electronically on or before 15 October 2013.

Boston College, a university of eight schools and colleges, is an Equal Opportunity Employer and supports Affirmative Action.

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start your career.
www.ScienceCareers.org

USC Davis
School of Gerontology

UNIVERSITY OF SOUTHERN CALIFORNIA

Davis School of Gerontology – Ethel Percy Andrus Gerontology Center

The USC Davis School of Gerontology and its Ethel Percy Andrus Gerontology Center are pleased to announce the next round in our continued expansion of tenure-track faculty. Our highly interdisciplinary faculty come from backgrounds in biochemistry, physiology, molecular biology, neuroscience, demography, psychology, sociology, urban planning, and public policy. In the current round, we seek to fill a tenure-track position at the Assistant Professor level with a biologist whose research encompasses mechanisms of aging, longevity, and/or age-related diseases. Biologists with expertise in molecular/genetic approaches and/or translational research are particularly encouraged to apply.

The successful candidates must have the capacity to thrive in our multidisciplinary research and teaching environment; they will be expected to develop a strong, independent research program supported by significant federal funding. We offer gerontology degrees at the bachelor's, master's, and doctoral level. Additionally, our diverse faculty members all have joint appointments in other schools and departments (e.g. molecular biology, neurobiology, psychology, *etc.*) where they also supervise Ph.D. students.

We actively encourage people of all backgrounds, ethnicity, and culture to apply. Candidates should send a C.V., along with a letter indicating research experience and plans for the future. They should also arrange for three letters of support to be sent to, **Gerontology Search Committee, Davis School of Gerontology, 3715 McClintock Avenue, Los Angeles, CA 90089-0191, USA**. Review of candidates will begin in **October 2013**, but will continue until a suitably qualified candidate is identified.

The University of Southern California is an Equal Opportunity Employer that Values Diversity.

UTSA The University of Texas at San Antonio

Robert A. Welch Endowed Chair in Chemistry at The University of Texas at San Antonio

The Department of Chemistry at The University of Texas at San Antonio (UTSA) invites nominations for its newly established Robert A. Welch Endowed Chair in Chemistry. Internationally renowned scientists whose research encompasses any area of modern chemistry will be given serious consideration. The Welch Chair includes a $3 million endowment, a highly competitive salary, and ample modern research space. Significant additional financial resources and state-of-the art facilities are available. The Welch Chair is expected to play a leadership role in our ongoing, aggressive departmental growth and faculty recruitment efforts. Opportunities are available for establishment and expansion of collaborative initiatives with nationally renowned area institutions, including the University of Texas Health Science Center at San Antonio and the Southwest Research Institute.

San Antonio, the 7th largest city in the U.S., features a historical and vibrant downtown area. UTSA is located northwest of downtown San Antonio adjacent to the scenic Texas Hill Country, which provides many recreational opportunities.

Self-nominations are encouraged. Nominations can be sent directly to the **Department Chair, Dr. Waldemar Gorski, at the following address: Department of Chemistry, UTSA, One UTSA Circle, San Antonio, TX 78249** or via email (**Waldemar.Gorski@utsa.edu**).

FAS Center for Systems Biology

Harvard University
FAS Center for Systems Biology
Faculty Position

The Faculty of Arts and Sciences (FAS) Center for Systems Biology (h**ttp://sysbio.harvard.edu/csb**) seeks outstanding candidates for a faculty position at the rank of assistant professor (tenure track). The Center, whose common research space houses faculty from a spectrum of academic departments and the Bauer Fellows, fosters interactions across disciplinary boundaries. We are interested in candidates involved in research in systems biology, using either experimental or computational approaches. A doctorate in a relevant discipline is required.

The successful candidate will hold an academic appointment in a FAS natural science department such as, but not restricted to, Molecular and Cellular Biology, Organismic and Evolutionary Biology, Physics or Chemistry and Chemical Biology. Faculty associated with the Center for Systems Biology have access to facilities and opportunities for collaborative research through the Bauer Core facilities, the Center for Nanoscale Systems, the Broad Institute, and the Center for Brain Science.

Applications, including letters of reference, are due by **November 15, 2013**. Please submit a CV, statement of research (up to 5 pages, including a summary of previous research accomplishments), teaching statement and PDFs of up to 3 publications to **http://academicpositions.harvard.edu/postings/4938**. All files must be submitted electronically in PDF or Word format. During the application process you will be asked to give the e-mail addresses of at least three colleagues who have agreed to write letters of recommendation for you. Please allow at least 1 week for your referees to upload their letters.

Applications from, or nominations of, women and minority candidates are encouraged. Harvard is an Affirmative Action/Equal Opportunity Employer.

BRAINS

Diversifying Neuroscience

Are you a postdoctoral scholar or assistant professor in a neuroscience-related field?

Do you identify as someone from a group underrepresented in neuroscience?

Are you interested in receiving in-depth career support and direction over a two-year period?

Join the BRAINS professional development program

Applications for the next cohort open in 2014

Visit brains.washington.edu

E-mail brains@uw.edu

In order to be eligible to participate in BRAINS, you must be a citizen or permanent resident of the United States and from a group or background recognized as underrepresented in neuroscience. Please visit our website for detailed eligibility information. Program Funded by NINDS Grant 1R25NS076416-01

Tenure-track Faculty Position

The BioFrontiers Institute at the University of Colorado in Boulder is looking for its next interdisciplinary faculty member.

We invite applications from candidates seeking to develop an internationally recognized research program in regenerative medicine addressing significant problems in areas related to stem cell research, biomaterials, tissue engineering, drug delivery, optical imaging, cellular biomechanics, or platform development for translational medicine.

BioFrontiers integrates faculty from nine departments (see **http://BioFrontiers.colorado.edu/About**). While a successful candidate could be rostered in any of these departments, the current search is particularly aimed at recruiting candidates with backgrounds and interests aligned with engineering disciplines. The position is at the Assistant Professor level, although senior candidates at Associate and Full Professor ranks will also be considered. Candidates must have a Ph.D. and a demonstrated commitment to teaching at undergraduate and graduate levels.

Learn more and apply online at **http://BioFrontiers.colorado.edu/facultyhire**. Address your letter of application to **Professor Kristi Anseth**. Review of applications will begin on **November 18, 2013**, and will continue until the position is filled. The University of Colorado is committed to diversity and equality in education and employment and sensitive to the needs of dual career couples

Application materials are accepted electronically at **https://www.jobsatcu.com/postings/70854**.

The University of Colorado Boulder conducts background checks for all final applicants. The University of Colorado is an Equal Opportunity/Affirmative Action employer.

BioFrontiers Institute
UNIVERSITY OF COLORADO
BOULDER | COLORADO SPRINGS | DENVER | ANSCHUTZ MEDICAL CAMPUS

PENNSTATE
1855

Faculty Position in Microbiology
Department of Biochemistry and Molecular Biology
The Pennsylvania State University

The Department of Biochemistry and Molecular Biology at Penn State invites applications for a tenure-track position in Microbiology at the **ASSISTANT Professor** level. Meritorious applications at higher levels will also be considered. We seek an outstanding individual who uses contemporary molecular approaches to investigate important processes in any area of microbial metabolism, physiology, genetics, pathogenesis, and ecology, and who utilizes organisms that belong to the domains *Bacteria* or *Archaea*. Candidates who employ systems-level approaches, including genomics and bioinformatics, metagenomics, and quantitative approaches to understanding important global processes, microbiomes, or biofuels are encouraged to apply. The successful candidate will have the opportunity to participate in appropriate centers, including Infectious Disease Dynamics, Comparative Genomics and Bioinformatics, RNA Molecular Biology, Astrobiology and the Institutes for Energy and the Environment. The position will feature a competitive start-up package and full access to university-subsidized research support facilities, including genomics, DNA core, X-ray crystallography, high-throughput calorimetry, high-field NMR, mass spectrometry for proteomics and metabolomics, electron and confocal microscopy, flow cytometry and fermentation (**http://www.huck.psu.edu/**). The successful candidate will be expected to direct an innovative, well-funded research program, to contribute to the teaching mission of the department, and to participate actively in service. Candidates qualified to teach microbial physiology, microbial genetics, microbial ecology and diversity and/or medical microbiology/pathogenesis are especially encouraged to apply.

Applications should be submitted as a single PDF document *via* email to Traci Shimmel (**tshimmel@psu.edu**). Documents should include *curriculum vitae* as well as a description of research interests and teaching goals (2-3 pages). Applicants should arrange to have three letters of reference sent to Traci Shimmel (**tshimmel@psu.edu**). Review of applications will begin **November 1, 2013** and will continue until the position is filled.

Penn State is committed to Affirmative Action, Equal Opportunity and the diversity of its workforce.

UT SOUTHWESTERN MEDICAL CENTER

Assistant Professor of Biochemistry

The Department of Biochemistry at The University of Texas Southwestern Medical Center invites applications from candidates for a tenure-track faculty position at the rank of Assistant Professor. Candidates should be engaged in innovative research within the broad fields of biochemistry or molecular biology. UT Southwestern maintains state-of-the-art facilities and employs a faculty that includes five Nobel Laureates and nineteen members of the National Academy of Sciences. The Biochemistry Department offers a vibrant environment for research, generous start-up support, and participation in graduate-level teaching. Applicants should submit a *curriculum vitae*, a concise description of research plans, and three letters of reference by **November 1, 2013** to the attention of Dr. Steven L. McKnight, Chair, Department of Biochemistry at **Biochem.Search@UTSouthwestern.edu**.

UT Southwestern Medical Center is an Affirmative Action/Equal Opportunity Employer. Women, minorities, veterans and individuals with disabilities are encouraged to apply.

IOWA STATE UNIVERSITY
Where you can become your best.

Assistant Professor Position in Bioinformatics and Computational Biology

The department of Genetics, Development and Cell Biology (**http://www.gdcb.iastate.edu**) at Iowa State University invites applications for a tenure-track position at the Assistant Professor level. We seek creative individuals employing genomic or interdisciplinary approaches to address fundamental questions. Applicants must have a Ph.D. and have demonstrated potential for superior achievement in research and teaching. The successful candidate will establish a program of **biological research and teaching, with an emphasis on bioinformatics or computational biology**. Successful candidates will establish vibrant, extramurally funded programs of research, will demonstrate an ability to work collaboratively within existing research strengths at ISU, and will contribute to undergraduate and to graduate courses in their area(s) of expertise through scholarly teaching.

Application instructions are at **http://www.iastatejobs.com** (vacancy 130917). Applicants should submit a cover letter, CV, and research and teaching statements by **14 October 2013**. Submission of three confidential letters of recommendation should be arranged as per instructions in the on-line application system.

ISU values diversity and is an AA/EEO Employee.

Tufts UNIVERSITY

Tufts University, Department of Biomedical Engineering – seeks candidates for a tenure-track faculty position at the Assistant or Associate Professor level, with rank determined by experience and accomplishments. Truly exceptional senior candidates may also be considered for appointment at the rank of Full Professor. Preference will be given to candidates whose research interests involve regenerative medicine, medical imaging, and biomedical optics, but all areas of biomedical engineering will be considered. The successful candidate will join an active department that offers B.S., M.E., M.S. and Ph.D. programs, and thus must demonstrate the potential to develop an outstanding, internationally recognized research program, excel in teaching, and develop strong interschool collaborations. Teaching responsibilities include graduate and undergraduate courses. A doctorate is required and postdoctoral experience is desirable. Additional information about the department can be found at **engineering.tufts.edu/bme/**. Interested applicants should send their Curriculum Vitae, cover letter, research plan, and names of three references to: **Faculty Search Committee, Department of Biomedical Engineering, Tufts University, 4 Colby Street, Medford, MA 02155**. Evaluation of candidates will begin at the end of **October 2013** and continue until the position is filled.

Tufts University is an Affirmative Action/Equal Opportunity Employer. We are committed to increasing the diversity of our faculty. Applications from women and members of underrepresented groups are strongly encouraged.











Hiring Vice President at South University of Science and Technology (SUSTC)Shenzhen, China

The South University of Science and Technology, China (SUSTC) invites applications and nominations for Vice President (Academic Affairs) and Vice President (Education). SUSTC is committed to **excellence in teaching and research**; therefore, it offers internationally competitive salaries, fringe benefits, retirement and housing subsidy to the Vice Presidents. The modern campus also offers pleasant working conditions.

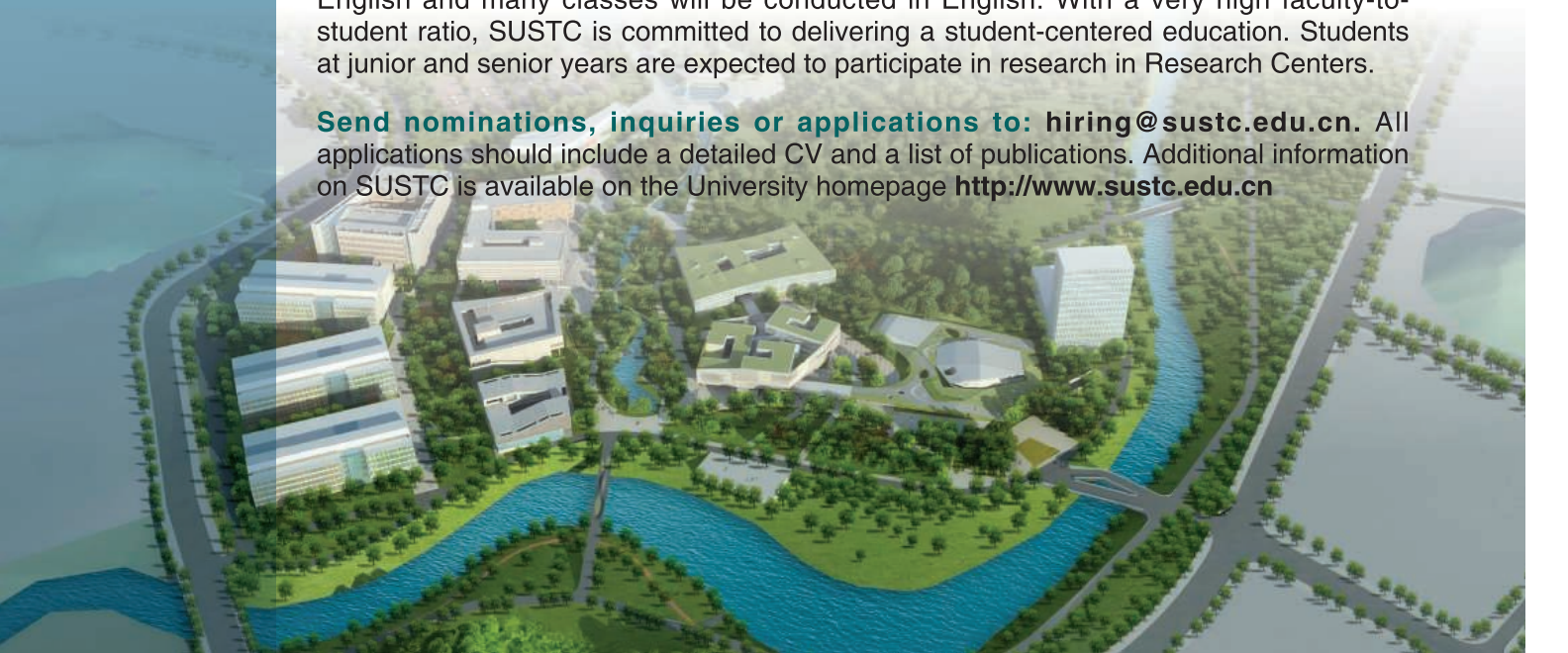
About SUSTC

SUSTC is a public institution funded by the municipal of Shenzhen, a special economic zone city in southern China. The University receives full financial support from the municipal. Set on five hundred acres of wooded landscape in the picturesque Nanshan (South Mountain) area, the campus offers an idyllic environment suitable for learning and scholarship. SUSTC engages in basic and problem-solving research of lasting impact to benefit society and mankind. Key research areas of the university include but not limited to: *Neural and Cognitive Sciences, Biology and Gene Engineering, Modern Physics, Control and Modification of Materials, Nanoscience and Nanotechnology, Mathematics and Applied Mathematics, Molecular Chemistry and Catalysis, Large-Scale Computational Research, Robotics and Artificial Intelligence, Information Systems and Electronic Engineering, Modern Cities and future developments, Energy Sciences and technology, Environmental Sciences, Financial Mathematics and Engineering.*

The Vice President (Academic Affairs, VPAA) and Vice President (Education, VPE) report directly to the president. The **VPAA** provides strategic leadership in the development and implementation of academic and research programs. The **VPE** provides strategic leadership in student education and whole person development. Successful candidates are expected to be internationally renowned scholars with administrative experience and good communication skills. Excellent leadership and organizational skills are also important.

The teaching language at SUSTC is English or Putonghua. As we expect an international faculty, the majority of teaching materials and reference books will be in English and many classes will be conducted in English. With a very high faculty-to-student ratio, SUSTC is committed to delivering a student-centered education. Students at junior and senior years are expected to participate in research in Research Centers.

Send nominations, inquiries or applications to: hiring@sustc.edu.cn. All applications should include a detailed CV and a list of publications. Additional information on SUSTC is available on the University homepage **http://www.sustc.edu.cn**





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To learn more, visit **aaas.org/plusyou/sciencecareers**

AAAS + U = Δ

AAAS

ADVANCING SCIENCE, SERVING SOCIETY

The American Association for the Advancement of Science (AAAS) is a non-profit organization dedicated to serving society through the advancement of science. The *Science* Research Journals are seeking a lively, detail-oriented **Editorial Coordinator** to work with a small team of editors in our Washington DC office. This is an excellent opportunity for a computer-comfortable individual interested in scholarly publishing to gain broad exposure to and experience in many aspects of publishing.

Major duties and responsibilities:

- Manage the production, scheduling, and tracking of our published articles, including monitoring content for adherence to style and format criteria
- Generate XML files
- Maintain documentation of procedures
- Provide other administrative support for the team, as assigned

Minimum requirements:

- Extensive university or college level training leading to a Bachelor's degree in a relevant field
- Two to three years of experience in an office environment
- Excellent written and oral communication skills including interaction with scientific authors
- Strong computer skills, particularly in Word and Excel
- Familiarity with copyediting is a plus

Please visit our job information website **http://www.aaas.org/careercenter/employmentataaas/** to get more information, and to apply to AAAS online.

AAAS is an Equal Opportunity Employer.

Project 2061 AAAS

The American Association for the Advancement of Science (AAAS) seeks a Research Assistant to support initiatives within Project 2061. Project 2061 is a long-term initiative of the American Association for the Advancement of Science (AAAS) to help all Americans become literate in science, mathematics, and technology. To achieve that goal, Project 2061 conducts research and develops tools and services that educators, researchers, and policymakers can use to make critical and lasting improvements in the nation's education system. The position offers the opportunity for individuals with a deep understanding of basic science ideas and the ability and interest in communicating those ideas to work at the national level to improve the science literacy of all.

This position is offered for a one-year period to be renewed contingent on grant funding.

Application materials should be received by November 1, 2013.

Major duties and responsibilities:

- Assist in developing test questions to assess students' understanding of evolution and related mathematics skills
- Identify research studies and data sets from the scientific literature that can be used as contexts for assessment development
- Work with senior staff to develop test questions that align with the targeted ideas and skills
- Prepare and administer pilot tests of the questions to collect data on how well the questions probe student understanding of those targeted ideas and skills
- Participate in data analysis and revision of the pilot test questions
- Maintain a database of test questions and student responses

*Information about Project 2061's assessment work can be found at **http://assessment.aaas.org/**

Minimum qualifications:

- Extensive university or college level training leading to a Bachelor's degree in biology or biochemistry; must have taken courses in evolutionary biology, genetics, and statistics
- Strong analytical, organizational, and writing skills and the ability to work well in a team environment
- Excellent computer skills including solid knowledge of Microsoft Excel spreadsheets and databases, basic statistical packages, and transferring test questions to a web accessible format
- Prior teaching experience at the K-12 level is desirable but not required

*Please include your CV/resume and cover letter with your application. Grade transcripts and three letters of recommendation are should be sent to **jobs@aaas.org**. Please visit our job information website **http://www.aaas.org/careercenter/employmentataaas/** to get more information, and to apply to AAAS online.

AAAS is an Equal Opportunity Employer.

Women in Science Booklet

Science and the L'Oréal Foundation present



Read inspiring profiles of women making a difference in biology.

Free download at ScienceCareers.org/LOrealWIS

MRC Laboratory of Molecular Biology

Cambridge, UK

Programme Leaders in Neurobiology

The Division of Neurobiology of the Medical Research Council Laboratory of Molecular Biology (MRC-LMB) wishes to recruit outstanding scientists who will develop an independent programme of research in the area of neurodegenerative diseases, with an emphasis on molecular/cellular mechanisms. Synergy with existing research programmes would be an advantage, but scientific excellence and the potential for major impact are paramount. Current research in the Division includes protein misfolding in relation to neurodegenerative diseases, mechanisms of synaptic transmission and vesicle recycling, as well as neural circuits, including sensory and motor processing, and circadian rhythms (www2.mrc-lmb.cam.ac.uk/NB/).

The LMB provides an excellent environment for hands-on research, with a new building providing outstanding facilities. The MRC has made a major investment in Neurobiology at the LMB, supporting the expansion of research in areas including neural circuits and neurodegenerative diseases, in addition to existing programmes. The MRC provides long-term support for ambitious and demanding projects, while administrative duties are minimal and no teaching is required. Interactions across the four Divisions of the LMB are encouraged. There is extensive central support, including electronic and instrumentation workshops, imaging and transgenic mouse facilities. The University of Cambridge and affiliated institutions form a vibrant Neuroscience community (http://www.neuroscience.cam.ac.uk/).

Candidates should have a PhD and/or MD and will have completed a period of postdoctoral training or equivalent, with an excellent track record, and show outstanding potential for independent research. The successful candidate will lead a small team and substantial funding will be available.

These appointments will be made at either Programme Leader-track or Programme Leader level, depending on achievements and experience. Programme Leader-track appointments will be made for those who demonstrate the potential to develop into Programme Leaders within six years. Candidates for Programme Leader positions should have a strong international track record of relevant independent research and a proven ability to lead a research team, pursuing original approaches to long-term research goals. Salaries are competitive (Programme Leader-track £35,935-£48,000 per annum; Programme Leader £47,699-£70,000 per annum).

These positions will remain open until they are filled; applications received by 15th October 2013 will be given priority.

Informal enquiries can be addressed to Michel Goedert (mg@mrc-lmb.cam.ac.uk). For further information about the MRC visit www.mrc.ac.uk

Applications should include a covering letter and full CV, an outline of current research interests (1 page) and a proposal for future research (up to 2 pages), along with the names and addresses of three professional referees who have agreed to be contacted prior to interview.

Applications are handled by the UK Shared Business Services Ltd; to apply please visit our job board at http://www.topcareer.jobs/Vacancy/irc107173_3525.aspx. If you are unable to apply online please contact 01793 867003 quoting reference IRC107173.

This position is subject to pre-employment screening
The Medical Research is an Equal Opportunities Employer No agencies please



Join the Conversation!

Twitter is a great way to connect with AAAS members and staff about the issues that matter to you most. Be a part of the discussion while staying up-to-date on the latest news and information about your personal member benefits.

Follow us @AAASmember and join the conversation with #AAAS

AAAS MemberCentral

MemberCentral.aaas.org

天津大学 Tianjin University





Tianjin University (TU) – School of Pharmaceutical Science and Technology (SPST) initiates an international faculty recruitment campaign with the goal of building a world-class school comprising global talent, a cosmopolitan environment and state-of-the-art infrastructure.

We seek junior and senior scholars with a demonstrated high level of excellence in research and dedication to teaching in English, to help build two major platforms: the **Institute of Drug Innovation and Development; and, the Institute for Molecular Design and Synthesis.**

Outstanding talent in all areas of pharmacy and molecular science are sought (e.g, pharmaceutics, pharmacology and toxicology, structural biochemistry, chemical biology, biochemical engineering, pharmaceutical process and formulation, pharma economics, regulatory science, public health policy, computational chemistry and biology, and material science).

SPST is a signal program of the new Tianjin campus development plan, housed in building 24 of the main Tianjin campus and outfitted for the highest international standard of modern research.

The program will be run in English for research, teaching and internal administrative activities. Student recruitment at the graduate (MS and PhD) level will be internationally competitive; the undergraduate program will provide top class instruction in English and a broad-based liberal education experience accessible to an international and Chinese student body.

Does this progressive and forward looking development interest you? Can you see yourself as a productive member/partner of the team that will realize this vision? Do you know an investigator who meets the high standards TU desires? Then contact us at **infospst@tju.edu.cn**

For full consideration, please submit before **September 22, 2013**, a current cv with personal references, a list of publications, a summary of research directions (2-3 pages), a statement of teaching interest (1 page) and up to 3 exemplary publications as a **single pdf file** [*LASTNAME_firstname_SPST_candidate.pdf*]

Competitive candidates will be invited to participate in SPST's *Symposium on Directions in Modern Pharmaceutical Science December 5-8 2013.*

TU-SPST is looking to find talent ready to change the landscape of higher education in China. Are you ready to be an element of change?

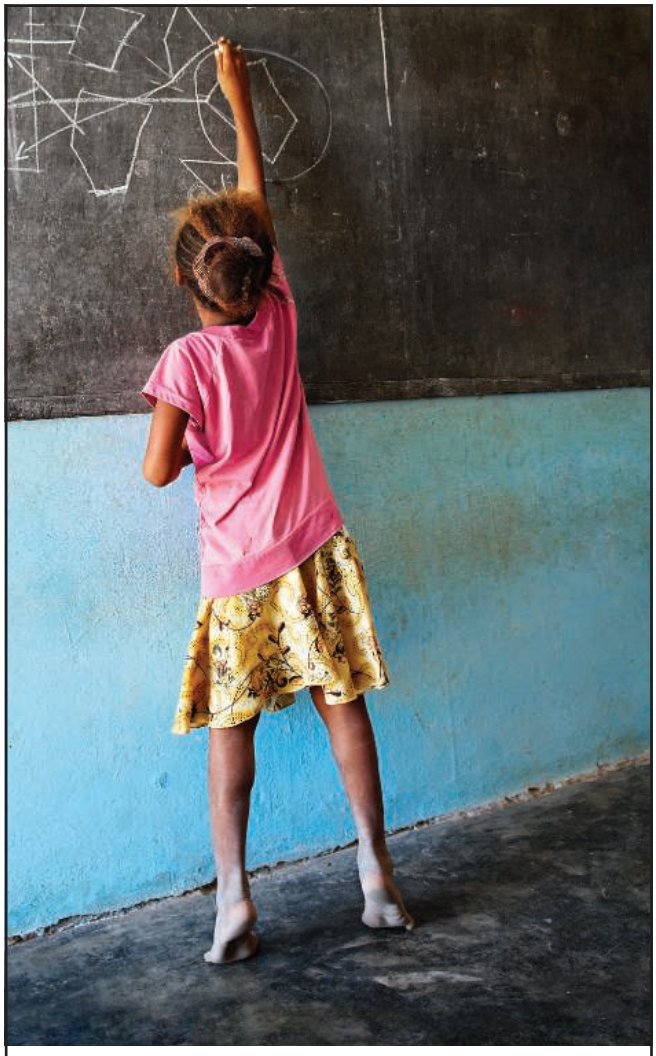


AAAS is here – Science Funding, Climate Regulation, Human Rights.

Around the world, governments turn to AAAS as an objective, multidisciplinary scientific authority to educate public officials and judicial figures on today's most pressing issues. And this is just one of the ways that AAAS is committed to advancing science to support a healthy and prosperous world. Join us. Together we can make a difference.

To learn more, visit **aaas.org/plusyou/policy**

AAAS + U = Δ



AAAS is here –

bringing educational infrastructure to the developing world.

AAAS is helping the Rwandan government rebuild its educational infrastructure as a way to help drive economic growth and development. By providing materials such as the Project 2061 *Atlas of Science Literacy*, lesson plans from Science NetLinks, and access to *Science* digital libraries, AAAS is helping the people of Rwanda work toward a future built around science and technology. As a AAAS member your dues support these efforts. If you're not yet a AAAS member, join us. Together we can make a difference.

To learn more, visit
aaas.org/plusyou/rwanda

AAAS + U = Δ

THE UNIVERSITY OF QUEENSLAND

Postdoctoral Fellowships, PhD Scholarships in CORAL REEF ECOSYSTEMS CLIMATE CHANGE

The School of Biological Sciences and the Global Change Institute at The University of Queensland (UQ) are pleased to announce opportunities for talented students and postdoctoral fellows in the following areas:

1. Coral reef ecology and climate change
2. Ecosystem dynamics and modelling
3. Ocean acidification and coral reefs
4. Computer vision and machine learning

Successful candidates will work with Professor Ove Hoegh-Guldberg and Associate Professor Sophie Dove at their Brisbane laboratories and at field locations in Australia (Heron Island) and globally. Applicants must demonstrate excellence in marine field and/or laboratory research, except in the last research area (computer vision and machine learning) where the emphasis is on developing software tools and strategies for extracting ecological information from photographic field observations. Peer-reviewed publications and other evidence of research capability will be viewed advantageously.

Full details of the projects and the positions can be found at **www.gci.uq.edu.au/projects/coral-reef-ecosystem-research-opportunities**. The research opportunities are supported by the ARC and Catlin Group.

UQ is located in Brisbane, Australia, and is internationally ranked in the world's top 100 universities by the Shanghai Jiao Tong, Times Higher Education, and QS. UQ is also one of Australia's Group of Eight, universities. For further details visit **www.uq.edu.au**.

Applications close 29 September 2013

Job No. 494949

Visit **www.uq.edu.au/uqjobs** for more career opportunities and to obtain a copy of the position descriptions and application process. UQ is an equal opportunity employer.

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uq.edu.au/uqjobs

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

CRICOS Provider Number 00025B

Science Careers



There's only one

Dr. Shirley Malcom

To Dr. Shirley Malcom, born and raised in the segregated South more than 65 years ago, a career based on her studies in science seemed even less likely than the launch of the Soviet's Sputnik. But with Sputnik's success, the Space Race officially started and, in an instant, brought a laser-like focus to science education and ways to deliver a proper response. Not long after, Dr. Malcom entered the picture.

Although black schools at the time received fewer dollars per student and did not have sufficient resources to maintain their labs at a level equivalent to the white schools, Dr. Malcom found her way to the University of Washington where she succeeded in obtaining a B.S. in spite of the difficulties of being an African American woman in the field of science. From there she went on to earn a Ph.D. in ecology from Penn State and held a faculty position at the University of North Carolina, Wilmington.

Dr. Malcom has served at the AAAS in multiple capacities, and is presently Head of the Directorate for Education and Human Resources Programs. Nominated by President Clinton to the National Science Board, she also held a position on his Committee of Advisors on Science and Technology. She is currently a member of the Caltech Board of Trustees, a Regent of Morgan State University, and co-chair of the Gender Advisory Board of the UN Commission on Science and Technology for Development. She has held numerous other positions of distinction and is the principal author of *The Double Bind: The Price of Being a Minority Woman in Science*.

Of her active career in science, Dr. Malcom says, "I guess I have become a poster child for taking one's science background and using that in many other ways: we ask questions; we try to understand what we find; we consider what evidence we would need to confirm or refute hypotheses. And that happens in whatever setting one finds oneself."

At *Science* we are here to help you in your own scientific career with expert career advice, forums, job postings, and more — all for free. Visit *Science* today at **ScienceCareers.org**.



AAAS

For your career in science, there's only one Science

ScienceCareers.org

Career advice | Job postings | Job Alerts | Career Forum | Crafting resumes/CVs | Preparing for interviews

PRIZES

Call for Nominations: Scolnick Prize in Neuroscience

The McGovern Institute for Brain Research is accepting nominations for the 11th annual Edward M. Scolnick Prize in Neuroscience. The Prize recognizes an outstanding discovery or significant advance in the field of neuroscience. The prize is $100,000. The recipient presents a public lecture at MIT, hosted by the McGovern Institute and followed by a dinner in Spring 2014.

Nomination Deadline: December 15, 2013

Nomination procedures: Candidates for the award must be nominated by individuals affiliated with universities, hospitals, medicals schools, or research institutes, with a background in neuroscience. Self-nomination is not permitted. Each nomination should include: • A biosketch or CV of the nominee; • A letter of nomination with a summary and analysis of the major contributions of the nominee to the field of neuroscience. • Up to two representative reprints will be accepted.

Selection Procedure: • Members of the selection committee and faculty affiliated with MIT are not eligible. • Announcement of the award recipient will be made in January 2014. • Recipient must attend all events to be awarded the prize.

Past Scolnick Prize Recipients:

2004: Dr. Masakazu Konishi, California Institute of Technology
2005: Dr. Judith L. Rapoport, National Institutes of Mental Health/NIH
2006: Dr. Michael E. Greenberg, Children's Hospital/HMS
2007: Dr. David Julius, University of California, San Francisco
2008: Dr. Michael Davis, Emory University School of Medicine, Atlanta
2009: Dr. Jeremy Nathans, Johns Hopkins University
2010: Drs. Lily and Yuh-Nung Jan, UCSF
2011: Dr. Bruce McEwen, The Rockefeller University
2012: Dr. Roger Nicoll, University of California, San Francisco
2013: Dr. Thomas Jessell, HHMI, Columbia University Medical Center

Send nomination packet to: **Attn: Scolnick Prize Nomination, McGovern Institute for Brain Research, Massachusetts Institute of Technology, 77 Massachusetts Avenue 46-3160, Cambridge, MA 02139; or gwolf@mit.edu.**

For more information: **http://mcgovern.mit.edu**

AWARDS

Heineken PRIJZEN | PRIZES

Call for Nominations Heineken Prizes 2014

The scientific Heineken Prizes, 200,000 US dollars each, recognise and reward unique achievement in the fields of biochemistry and biophysics, medicine, history, environmental sciences and cognitive science. These biennial prizes are awarded by the **Dr H.P. Heineken Foundation** and the **Alfred Heineken Fondsen Foundation.**

The selection of the prize winners is entrusted to the **Royal Netherlands Academy of Arts and Sciences.**

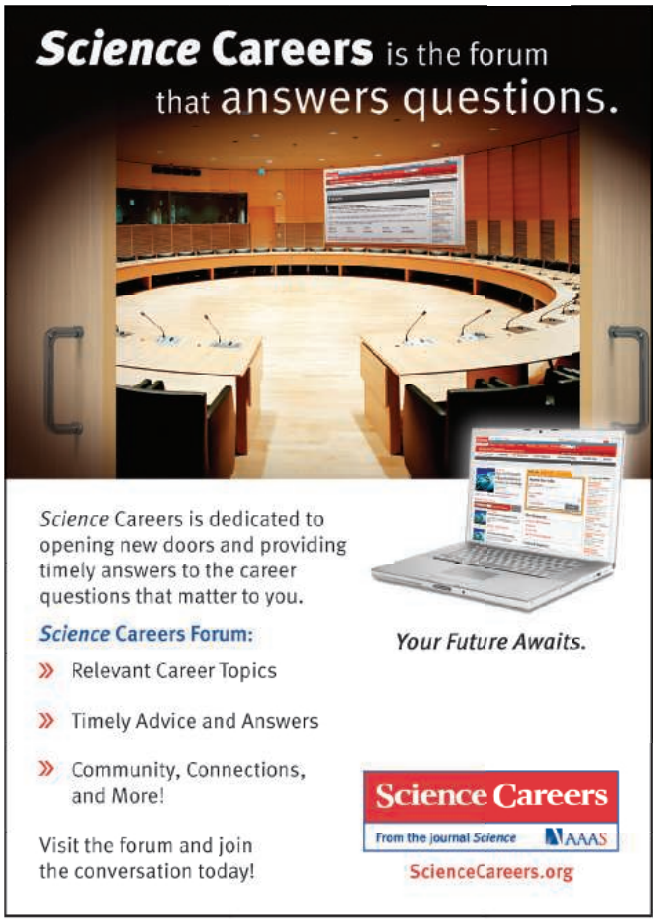
Many leading scientists, including a number of future Nobel laureates, have been honoured by the Academy for their pioneering research, such as:

- Jack W. Szostak
- Elizabeth H. Blackburn
- Jonathan I. Israel
- Simon A. Levin
- Stanislas Dehaene

Deadline for nominations is 15 November 2013

Visit our website **www.knaw.nl/heinekenprizes** for more information and the nomination form or contact us at: Royal Netherlands Academy of Arts and Sciences
T. +31 20 551 0859 | E. hp@knaw.nl

KNAW



PRIZES

19th MARCH OF DIMES PRIZE IN DEVELOPMENTAL BIOLOGY (2014)

The March of Dimes Prize in Developmental Biology is bestowed upon investigators whose research has profoundly advanced the science that underlies our understanding of birth defects. This $250,000 Prize values technical innovation as well as programmatic accomplishments.

Information on nomination procedure and a list of prior recipients are available upon request.

Nominations should be sent on or before
October 31, 2013 to:
Joe Leigh Simpson, M.D., FACOG, FACMG
Senior Vice President for Research and Global Programs
March of Dimes
1275 Mamaroneck Avenue
White Plains, NY 10605
Telephone: (914) 997-4555
Facsimile: (914) 339-2268
jsimpson@marchofdimes.com



AAAS is here – bringing scientific expertise to policy making.

Good science policy is the result of politicians understanding science and scientists understanding policy. Toward this end, AAAS manages the Science & Technology Policy Fellowships program, which embeds scientists and engineers in the federal government for up to two years. From Congress to the State Department, each class of Fellows contributes to the policy-making process while getting hands-on experience at the intersection of science and policy. As a AAAS member your dues support these efforts. If you're not yet a AAAS member, join us. Together we can make a difference.

To learn more, visit **aaas.org/plusyou/fellows**

AAAS + U = Δ